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ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Volume 61, Art. 1, Pages 1–280

Editor

Roy Waldo Miner

RESERPINE IN THE TREATMENT OF NEUROPSYCHIATRIC, NEUROLOGICAL, AND RELATED CLINICAL PROBLEMS

BY

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NEW YORK

PUBLISHED BY THE ACADEMY

April 15, 1955

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(Founded in 1817)

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Vol. 61
art. 1-4
1955

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
VOLUME 61, ART. 1, PAGES 1–280
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Editor
ROY WALDO MINER

RESERPINE IN THE TREATMENT OF NEUROPSYCHIATRIC, NEUROLOGICAL, AND RELATED CLINICAL PROBLEMS*

Conference Co-Chairmen: FREDRICK F. YONKMAN, FRANK L. MOHR, AND JOCK L. GRAEME

Consulting Editor: FREDRICK F. YONKMAN

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* This series of papers is the result of a conference on *Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems* held by the Section of Biology of The New York Academy of Sciences, February 3 and 4, 1955.

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INTRODUCTION

By Hilary Koprowski*

Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

An opportunity is presented in this introduction to describe briefly how conferences such as this are organized, since some of you might be interested in arranging a future conference on one subject or another under the auspices of The New York Academy of Sciences.

A subject is usually suggested to the Conference Organization Committee of the Academy by an individual scientist, or by a group of outstanding investigators, in a particular field. One of these men acts as chairman of a conference committee and, usually, but not always, becomes chairman of the conference. The Academy's Conference Organization Committee examines the tentative plan for the conference, inquires as to the purpose, scope, *etc.*, and may then note a preliminary approval. From then on, the chairman and the conference committee are on their own. It is his or their privilege to choose the speakers, to organize the sessions, and to see that different approaches to the main problem are adequately represented. The final program is submitted for approval to the Academy's Conference Organization Committee, which notes, after careful scrutiny, its final acceptance, and forwards a resolution to the Council of the Academy, for its official and final approval.

In spite of this routine, it is not a simple task to organize a conference. The chairman and his committee have to work hard, and the results are not always personally gratifying. There are always a few persons who, either as individuals or as representatives of organizations, consider it a humiliating discourtesy on the part of the chairman and his committee not to be invited to speak at a conference. No such discourtesy, however, is intended. It is impossible to ask everybody to participate who works in a given field of scientific endeavor. Any chairman attempting to do so would risk staying at the Barbizon-Plaza for weeks, and perhaps for months, instead of two days. The Academy relies on his good judgment to choose as official speakers those who have the most to contribute. At the same time, the Academy feels that progress in science can be maintained only if the right to dissent is recognized. Anyone who does not agree with an approach to the problem presented by an invited speaker is encouraged to come to the conference and take part in the discussion. It is often the discussion from the floor which "puts things across" and contributes to the success of a conference. However, nobody knows all the answers, since, according to C. P. Snow, "the real point about science is not that it knows the right answers but the right questions."

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* Chairman, Section of Biology, The New York Academy of Sciences.

SIGNIFICANCE OF SELECTED CENTRAL MECHANISMS FOR THE ANALYSIS OF THE ACTION OF RESERPINE

By H. J. Bein
Research Department, Ciba Ltd., Basle, Switzerland

Reserpine, a pharmacologically and clinically very potent ester alkaloid from *Rauwolfia*, exhibits a complex pattern of activity; there is a *syndrome* of effects and, while the majority of the components can be regarded as due to central action, there are also some which are peripheral or partly peripheral in nature (Bein, Gross, Tripod, and Meier, 1953; Plummer, Earl, Schneider, Trapold, and Barrett, 1954). The individual components are also complex in structure. Characteristic features of reserpine are its sedative and hypnotic effects of a peculiar type—which differ from those of the known substances possessing central inhibitor activity—arterial blood pressure reduction with bradycardia, some respiratory inhibition, stimulation of peristalsis, miosis, relaxation of the nictitating membrane, and its effect on the temperature-regulating center (Bein, 1953). This pattern of symptoms corresponds in its form to a syndrome obtained by Hess (1954) upon electrical stimulation of certain diencephalic structures. An analogous clinical pattern combining individual components in a uniform picture is found in patients with tumors of the posterior hypothalamus (Fulton, 1943). The fact that reserpine sets off such a defined central complex of symptoms indicates that it influences apparently coordinatively linked and integrating central mechanisms while, at the same time, the question of the localization of its points of attack need not necessarily be implicated by such a consideration.

When an attempt is made to localize and elucidate the points of attack, it is of decisive importance if it can be shown that all the actions of reserpine operate independently of the function of peripherally situated mechanisms, but are absent or modified in the absence of certain defined central substrates. A particularly suitable example of the analysis of such a mechanism of action would be the analysis of the behavior of centrally transmitted autonomic impulses after stimulation of afferent nerves. In the field of the cardiovascular system, for instance, there are the "reflex" blood pressure increases which are susceptible to inhibition by reserpine. Depressor reactions triggered off in an analogous manner are not specifically influenced. In the field of the respiratory reflexes there are also certain processes that are influenced by reserpine (Serpasil) and that are particularly suitable for differentiation tests. This differentiation of the reflexes permits, at the same time, the deduction that the action of reserpine, even in the case of apparently similarly provoked effects, is characterized by a specific selection of reflexes.

The investigation of such autonomic reflex arcs thus offers the opportunity, first of all, of determining the point of attack of reserpine by establishing its effects upon the individual organizational stages of the reflex. The elucidation of possible central influences can be attempted either by direct observation, by the elimination of certain central elements, or of certain other points of attack.

As the elicitation of the carotid-sinus reflex gives rise to both blood pressure and respiratory reactions, these phenomena appear suitable as an example of such an analysis of a reflex.

Pressor carotid sinus reflexes in the cat anesthetized with Dial-urethan [Dial Ciba 30 mg./kg. intraperitoneally (i.p.) and 40 mg./kg. subcutaneously (s.c.)] are diminished after small doses of reserpine, such as 10 to 20 γ/kg. intravenously (i.v.), as in FIGURE 1. The eliciting mechanism and the target organ retain their reactivity unmodified. The reserpine inhibition also occurs when using the Moissejeff's carotid-sinus preparation (Koch, 1931), which is isolated from the general circulation and is connected to the organism by nervous pathways only. It is further shown that the activity of the pressor receptors is not inhibited by reserpine after systemic application, as can be demonstrated by oscillographic investigations of the sinus nerve. After complete division of the brain stem immediately caudal to the colliculi caudales, these same small doses of reserpine are ineffective. To obtain a corresponding diminution of the pressor carotid-sinus reflex in an animal decerebrated in this manner, it is usually necessary to give at least 20 times as large a dose of reserpine. A reflex response which has already been inhibited by the small doses is augmented again in the same animal after severing the brain stem.

An intact connection between medulla and midbrain is thus essential for one of the characteristic reserpine effects: when this connection is severed, reserpine can exert an analogous effect only after very much larger doses. The high doses, however, also affect those substrates responsible for the reflex effect that are situated caudally to the region of the quadrigeminal bodies. As a carotid-sinus reflex that is blocked by reserpine recuperates, at least in part, after dividing the brain stem, one may assume that the intact animal possesses one or several substrates that inhibit the pressor carotid-sinus reflex, and that, on their part, are "activated" by reserpine (Bein, Helmich and Meier, 1955). Our investigations cannot determine the localization of these mechanisms. It is possible that they should be sought rostral to the division, with pathways to the caudal substrates. There could also be an inhibiting substrate which extends over the entire brain stem, which, basically, would be accessible to reserpine over its whole extent, the function of which, however, would be blocked by the division mentioned earlier, *i.e.*, which could fulfill the function assumed by us only if intact.

The anatomical severance behind the quadrigeminal bodies also affects the drop in arterial pressure brought about by small doses of reserpine (10 to 20 γ/kg. i.v.); provided the operation is carried out very carefully and with an absolute minimum of trauma, the low pressure induced by reserpine can rise once more (FIGURE 1). A larger dose of reserpine again lowers the pressure: suitable doses of reserpine can thus also lower the pressure by attacking central substrates located more caudally. This is in agreement with earlier observations by Schneider (1954).

Although Tripod and Meier (1954) were able to demonstrate a considerable antagonism to pitressin and $BaCl_2$ in experiments on isolated circulatory organs and, since the possibility of a general spasmolytic component and a direct effect upon the vessel wall must thus be taken into consideration for the *in situ*

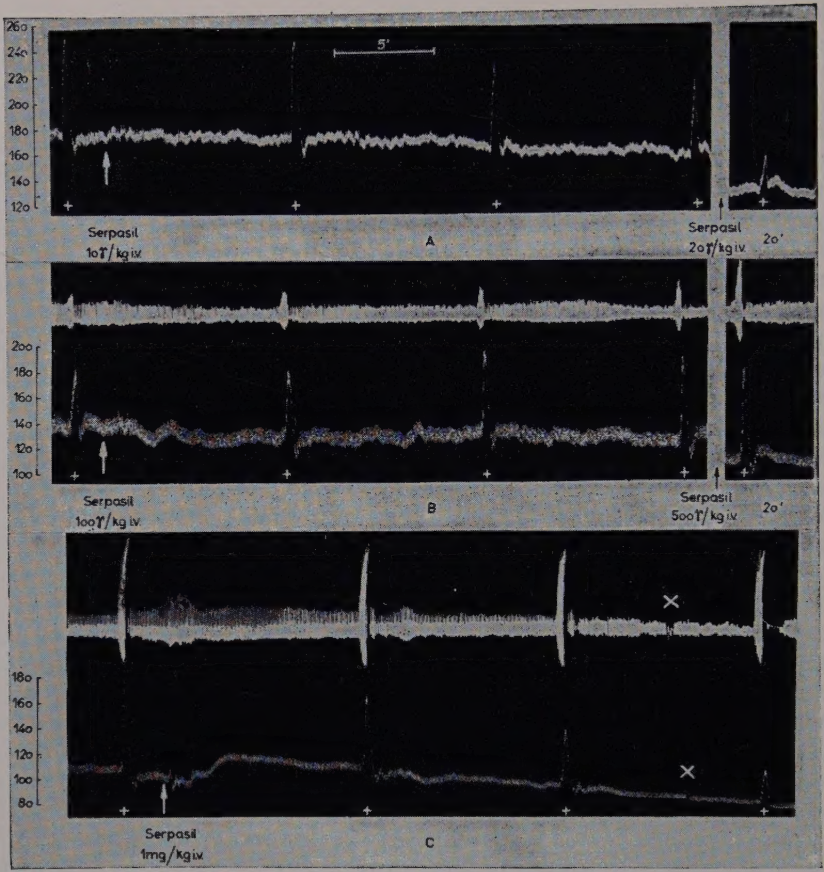

FIGURE 1. Cat: (dial anesthesia, vagus and depressor nerves bilaterally divided). Registration of the arterial pressure (graduation in mm. Hg outside left) taken from the common carotid artery, and elicitation of the pressor reflex of the carotid sinus by clamping the contralateral common carotid artery for 20 seconds. (+). *A*: before division, *B* and *C*: after division of the brain stem immediately caudal to the inferior colliculi at right angles to the axis of the brain stem. *A*, *B*, and *C* were obtained in the same experiment.

Prior to the division of the brain stem the pressor reflex is inhibited by small doses (10 γ/kg. i.v. dissolved in ascorbic acid) of reserpine (*A*, outside right: 20 minutes after 20 γ/kg. reserpine i.v.); after the brain stem has been severed not even 50 times this dose is able to inhibit the reflex (*B*, outside right: 20 minutes after 500 γ/kg. i.v.).

Note that the blood pressure, depressed by reserpine, rises again after section of the brain stem.

(× = technical disturbance)

pressure drop as well, a decrease of sympathetic impulses can also be regarded as one of the causative components. Oscillographic records, in fact, show a diminution of the sympathetic outflow in a sympathetic cardiac nerve occurring simultaneously with a bradycardic action (FIGURE 2). Excitation of the vagal system is not a likelihood, since no component inhibitable by atropine could be demonstrated, and a dependance on excitation of peripheral receptor fields analogous to the veratrine action is unlikely, since division of the vagus had no influence on the effect (Bein, 1953). A further confirmation of the mechanism of action under discussion is provided by a similar behavior of other effects, even if these others do not belong to the group of decisive or clinically signifi-

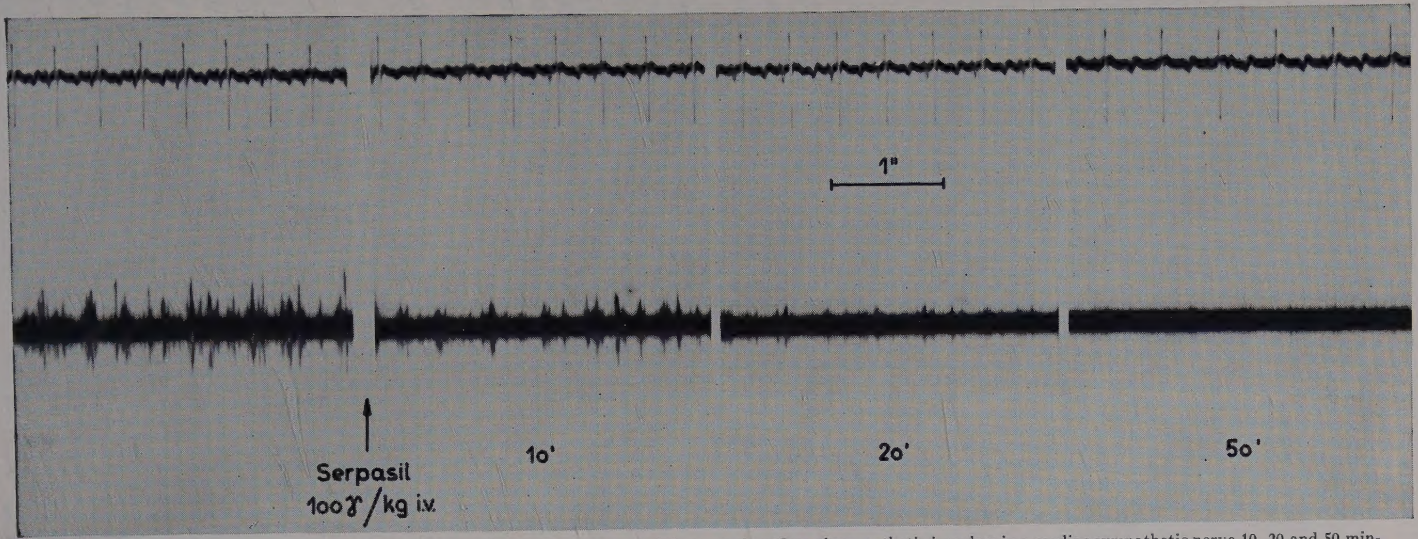

Figure 2. Cat: (anesthetized with Chloralose 80 mg./kg. i.v.). Decrease of the central outflow of sympathetic impulses in a cardiac sympathetic nerve 10, 20 and 50 minutes after reserpine 0.1 mg./kg. i.v. occurring simultaneously with bradycardia. Upper tracing: Electrocardiogram. Lower tracing: spontaneous discharge in a sympathetic cardiac nerve, peripherally sectioned.

cant reserpine effects. Because of its organizational structure, such an effect can serve as evidence in the problem under review. During the last few years, the nictitating membrane has received considerable attention as an experimental object for autonomic functions, since it lacks vagal innervation. Because of this absence of dual innervation, it thus provides a suitable indicator of sympathetic excitation. Quantitative parallelism between nictitating membrane and the circulation, for instance, is not to be expected, however, in view of the special central structure of the autonomic system (Morison and Rioch, 1937). Reserpine relaxes the nictitating membrane. In this test, reserpine possesses no ganglionic blocking and no peripheral sympathicolytic activity. The relaxation of the nictitating membrane under the influence of reserpine thus may be regarded as a sign of a centrally occasioned or transmitted diminution of the sympathetic tone. Even during relaxation, however, a cortically provoked stimulus is fully effective (FIGURE 3). We shall return to this finding later on. Blood-pressure increases resulting from cortical stimulation are not inhibited by reserpine even in the relatively high dosage of 1 mg./kg. i.v. (FIGURE 3). These rises and nictitating membrane contractions are transmitted by the sympathetic system and may be qualitatively characterized as adrenergic functions: they may be blocked by typical sympathicolytics [Dibenamine (Kell and Hoff, 1952), Regitine (our own observations)], and by specific ganglionic blockers [Pendiomide (Bein and Meier, 1954)]. These cortically-triggered sympathetic blood pressure rises and nictitating membrane contractions are also inhibited by general narcotics such as ether (Bein and Meier, 1954) and by barbiturates. In these cases, however, no peripheral point of attack can be demonstrated: blood pressure rises after intravenous injection of the neurohumoral transmitter substances (adrenalin, noradrenalin) and after electrical stimulation of an efferent path (splanchnic nerve) are not significantly blocked by ether or barbiturates in suitable dosage—in contrast to the cortical stimuli. The action of reserpine can be differentiated from that of the narcotics as regards seemingly somatic functions (Tripod, Bein and Meier, 1954). They can thus also be distinguished in their effects upon central autonomic substrates by their particular specificity.

The following may perhaps provide an explanation of the behavior of reserpine: Wall and Davis (1951) describe, in the monkey, sympathetic pathways of cortical origin, which, depending on their point of origin, lead to the periphery either in connection with the hypothalamus or independently. Landau (1953) assumes that in the pyramidal tracts of the cat there are autonomic pathways coming from the cortex that are independent of the hypothalamus. The existence of different central sympathetic substrates that are separable from each other must thus be assumed. This assumption opens up the possibility that the sympathetic inhibition with which reserpine produces relaxation of the nictitating membrane and perhaps a blood pressure fall may be classifiable as belonging to a central sympathetic substrate which differs from that to which belong the mechanisms excited by localized electrical stimulation of the sigmoid gyrus or of diencephalic structures [Schneider (1955) found that reserpine did not diminish the blood pressure rise found after electrical hypothalamic stimulation]. It must also be considered that electrical stimuli might

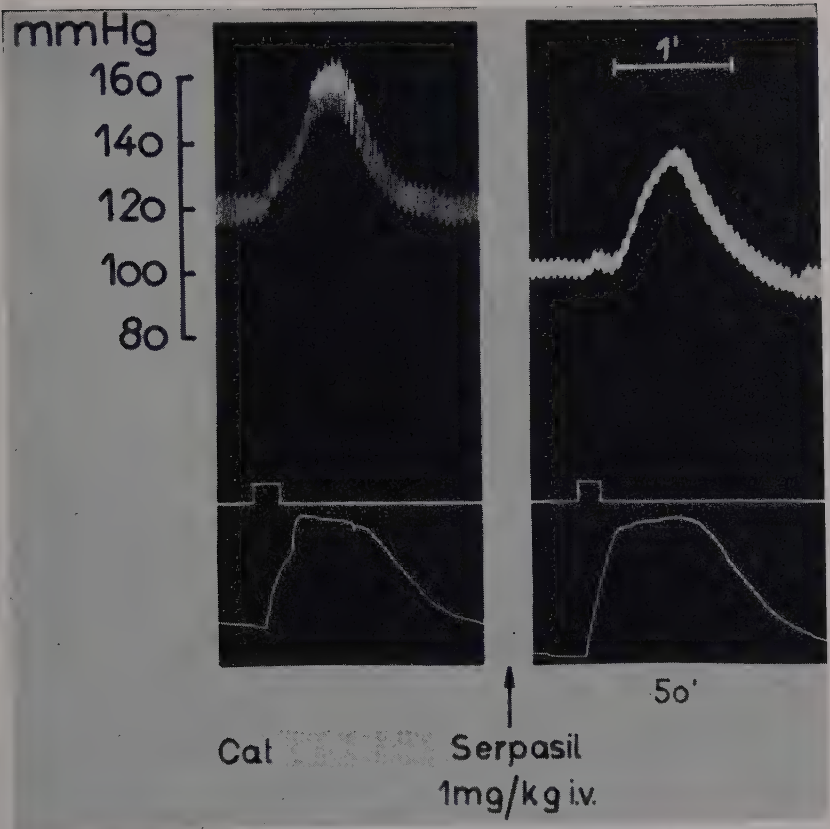

FIGURE 3. Cat: Electric stimulation of the left anterior sigmoid gyrus (method of Hoff *et al.*, 1951) for 10 seconds results in a blood pressure rise, and in a contraction of the nictitating membrane which is not inhibited by 1 mg./kg. reserpine i.v. Fifty minutes after the administration the arterial pressure has dropped and the nictitating membrane relaxed.

Top to bottom: pressure taken from the right femoral artery; stimulus signal; and myogram of the right nictitating membrane.

be able to break through the substrates inhibited by reserpine. An investigation of the threshold sensitivity to stimuli might serve to provide data on this point.

Such a differential action on the part of reserpine upon different central sympathetic mechanisms would signify that, even where the end effect is apparently the same and is brought about by apparently the same central mechanism (central excitation of the sympathetic nervous system), only certain forms would be capable of responding. There is also the possibility that various central or centrally transmitted stimuli might be distinguished by different peripheral mechanisms. Upon different central stimuli different relative contents of the adrenal venous blood in adrenalin/noradrenalin were noted (see Euler and Folkow, 1953). On the other hand, transmitter substances which are not identical with the ones identified to date may be involved in part. The activation of inhibiting substrates discussed earlier, using the pressor reflex of the carotid sinus as an example, could well prove applicable, however, for the entire reserpine action. Assuming this, the central inhibition of the sympathetic system by reserpine could be explained generally by secondary systems, while the direct sensitivity of the sympathetic mechanism or mechanisms need not necessarily be affected.

Particularly suitable for the further analysis of the possible mechanisms is the investigation of a reflex mechanism, such as that of the respiration, in which various chemical and physical, proprioceptive, and other mechanisms can be investigated.

Reserpine alters spontaneous respiration in a characteristic manner. The reason for this must presumably be sought in a modification of the neuroregulative factors of respiration.

In a manner resembling that of the inhibition of the blood pressure rises originating from the carotid sinus, small doses of reserpine (10 to 20 γ/kg. i.v.) inhibit the reflex respiratory changes found in connection with these rises, provided the brain stem has not been severed behind the inferior colliculus. The behavior is thus analogous to that of the pressor reflex. After division of the brain stem, these respiratory reflexes are not suppressed even by very high doses of reserpine (up to 3 mg./kg. i.v.—FIGURE 1). This is in some contrast to the pressor reflex, which is still inhibited by large doses of reserpine even after the division. Thus, this effect is a further example of the differential response to reserpine depending on the system stimulated, even though both actions of reserpine require an intact connection between rostral and caudal central substrates.

This behavior suggests that only certain respiratory reflexes are affected, the selection depending on point of attack and mechanism. The systematic investigation of a series of other respiratory reflexes, elicited in various ways, revealed pronounced differential responses to reserpine (for detailed results, see Meier and Bein, 1955).

Respiratory reflexes transmitted by the vagus [Head's tracheal occlusion reactions in Meier's modification for quantitative analysis (1940–1941), and also inspiratory and expiratory changes after electrical stimulation of the proximal cervical vagus that are predominantly dependent on the stimulation frequency and thus on the quality of the fibers stimulated (Wyss and Rivkine, 1950)] are not affected in the rabbit by reserpine. Reserpine is thus established as clearly different in action from morphine, morphinelike central analgesics, and barbiturates, which potentiate in a characteristic manner the vagal respiratory reflexes leading to expiratory reactions (Meier and Bucher, 1944; Bucher, 1944; Rickenbach and Meier, 1948).

In agreement with the findings obtained with Meier's tracheal occlusion reaction and, as further evidence that the reserpine effect does not depend on peripheral mechanisms, it was shown that reserpine does not modify the sensitivity of vagal pulmonary stretch receptors. (Oscillographic investigations of single fiber preparations of the pulmonary vagus *in situ* according to the technique of Bein and Helmich, 1949.) Reserpine can thus be differentiated from veratrine not only as regards the action on the circulation but also as regards the action on the respiration, since veratrine enhances the activity of the pulmonary stretch receptors, its effect on the respiration being at least partly explicable as a result of such a peripheral point of attack (Meier, Bein, and Helmich, 1949). Electrical stimulation of medullary substrates modifies the inspiratory or the expiratory phase of the respiration, depending on the localization of stimulation. Variation of the frequency of stimulation does not result in a qualitative modification of the response to stimulation, provided the intramedullary placing of the electrodes has been appropriate. There is thus a functional differentiation of these central substrates from afferent vagus fibers. The anatomical localization of these "inspiratory and expiratory substrates" in the reticular formation of the brain stem was described by Rickenbach and Meessen (1951) of our laboratories. Reserpine occasions no specific modification of the sensitivity of these systems to electrical stimuli, in spite of the fact that it clearly modifies the spontaneous respiration (FIGURE 4). Neither can a change in sensitivity ascribable to reserpine be demonstrated when the reactivity of these central substrates to electrical stimuli is modified in the rabbit with intact peripheral chemoreceptors by having it breathe a gas mixture rich in CO_2 (5 per cent CO_2, 20 per cent O_2, and 75 per cent N_2). These experiments thus exclude the possibility that reserpine influences the respiration by acting upon the vagal respiratory reflexes, the medullary "inspiratory and expiratory substrates," or the motor pathway and neuromuscular transmission respectively.

Reserpine, on the other hand, produces typical modifications of respiratory effects resulting from chemical stimulation. It was already mentioned in an earlier publication (Bein, Gross, Tripod, and Meier, 1953) that reserpine inhibits the augmentation of the respiration which results from the breathing of a mixture rich in CO_2 (5 to 10 per cent CO_2, 20 per cent O_2, and 75 to 70 per cent N_2). A peripheral inhibition by reserpine is unlikely, as oscillographic investigations of the chemoreceptors of the carotid sinus indicated no reduced reaction to CO_2 stimulus. Coramine is able to restore the original reactivity to CO_2. A similar restoration of the response of the respiratory substrates by Coramine was also found where the respiration was depressed with morphine (Meier and Müller, 1941). In spite of the difference between the mechanisms of action of morphine and reserpine, there are thus indications of a parallel effect exerted upon certain central substrates. A further possibility of analyzing the connection between physical/chemical reflex effects upon the respiration is provided by the analysis of hyperventilation apnea. In the rabbit anesthetized with Dial or urethan, small doses of reserpine ($70\,\gamma$/kg. i.v.) markedly shorten the duration of apnea after hyperventilation (with the Dale-Schuster pump) applied for two minutes (using air or O_2). In fact, it is not possible to render apneic rabbits treated with reserpine (FIGURE 5). Decerebration (immediately caudal of the inferior colliculi and more caudally, about 1 mm. below the brachia pontis), accompanied by bilateral vagotomy (simultaneous with brain stem division, and without this), does not modify this effect of reserpine either quantitatively or qualitatively. In the anesthetized cat (Dial Ciba 30 mg./kg. i.p. and 40 mg./kg. s.c., or urethan 1.25 g./kg. i.v.), reserpine shortened the period of apnea after hyperventilation in only one out of eight animals, so that, although the effect of reserpine on the respiration takes the

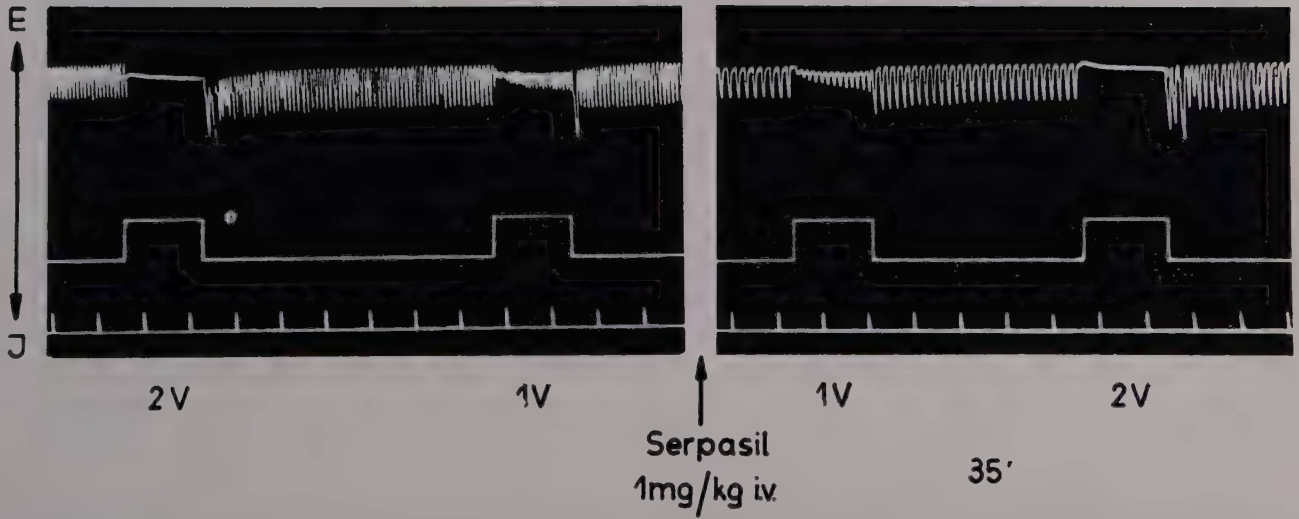

FIGURE 4. Rabbit: (anesthesia: urethan 1.5 g./kg. i.v.). Electrical stimulation in the medullary "expiratory substrate," varying intensities being applied (one volt, or two volts output of the Grass Stimulator) results in expiratory apnea. (Duration of stimulation: 10 secs., frequency: 100/sec., duration of the stimulus: 2 msec.).

Top to bottom: Respiration (E = Expiration; I = Inspiration).

Stimulus signal, timing marks: 6 secs. In spite of the slowing down of the respiration and diminution of the tidal volume 35 minutes after 1 mg./kg. reserpine i.v. no change of sensitivity to electrical stimulation occurs in the "expiratory substrate."

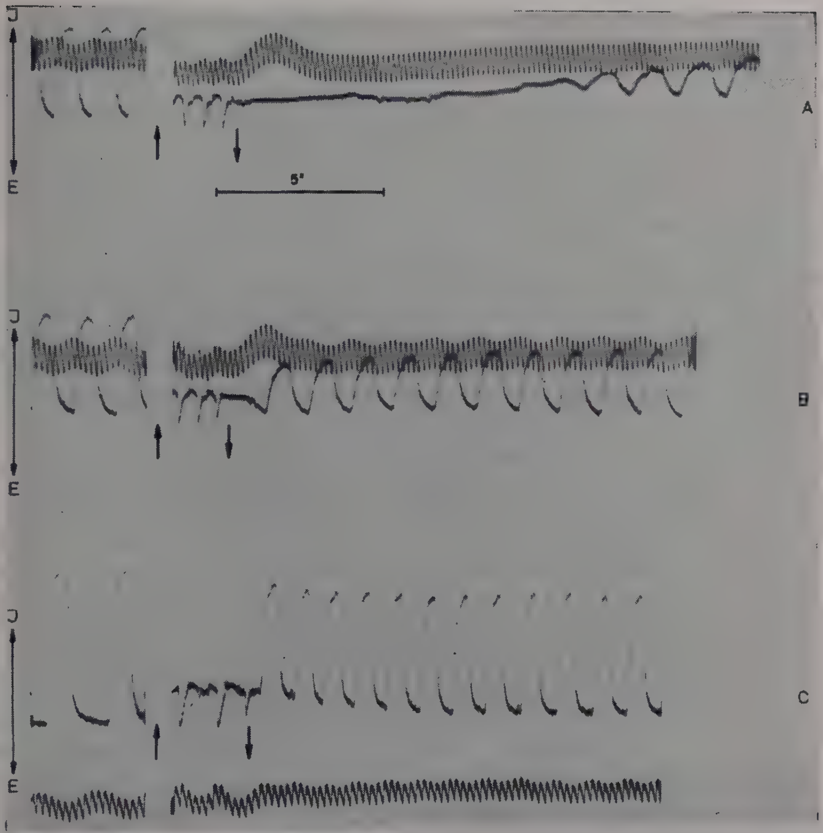

FIGURE 5. Rabbit: (urethan anesthesia; section of the brain stem caudally to the brachia pontis). Registration of the respiration with Bucher's body plethysmograph (Bucher, 1942), and registration of the arterial pressure.

The duration of the apnea after hyperventilation is shortened by reserpine, and the simultaneous blood pressure rise is diminished or inhibited.

Outside left, spontaneous respiration, *A:* before, *B:* 10 minutes after, and *C:* 110 minutes after 1 mg./kg. reserpine i.v.

Apnea after hyperventilation with O_2 for two minutes (↑). ↓ End of artificial respiration. Respirator frequency: 44/min., 30 cc. tidal volume.

The respiratory excursions registered during the hyperventilation phase are not to scale.

same form in these two species, different or additional points of attack must be assumed to play a part.

It can also be demonstrated, at least as regards this reflex-chemical process in the rabbit, that reserpine is able to exert an influence on caudally situated centers in small doses as well, and that, dependent on the substrate selected—*i.e.* on the choice of defined functional systems—it is able to manifest itself in the same dosage on both rostral and caudal central mechanisms.

A. Liljestrand (1953) has shown that CO_2 attacks special bulbar chemoreceptors in addition to peripheral chemoreceptors, *e.g.* of the carotid sinus, and that the siting of the former differs from that of the substrates responsible for apnea. Both of the central chemoreceptor substrates can be spatially delimited from the medullary "inspiratory and expiratory substrates," which can be characterized by electrical stimulation. Even within a single action component belonging to the manifold total complex of effects, reserpine is able to act only upon certain functional systems that can be delimited not only functionally but, within a relatively narrow field, anatomically as well.

Bonvallet, Dell, and Hiebel (1954) were recently able to demonstrate that the pressor reflex of the carotid sinus produced an activation of the EEG, and that the depressor carotid sinus reflex produced inactivation of the EEG. These effects are transmitted by a mesencephalic system which Bonvallet *et al.* regard as identical with the ascending reticular activating system of Magoun (1950, 1954) and Moruzzi (1954) which extends from the medulla to the rostral pole of the thalamus. The reticular systems regulate autonomic (Thompson and Bach, 1950) and somatic functions, are also controlled by the essential physicochemical factors of the respiration (CO_2/O_2) (Dell and Bonvallet, 1954), and seem to be one of the principal integrating systems. They are regarded as regulating the background activity of the remainder of the central nervous system, but are themselves also under the control of corticifugal influences. The ascending reticular system may not be entirely an activating system but may have inhibiting components as well, especially in the mesodiencephalic portion (Jasper, 1954). There is also evidence that there might be a high degree of specificity in the reticular systems (Jasper, 1954).

As regards closely delimited somatic symptom complexes, reserpine is able to act only upon certain functional systems. In the mouse, for instance, increases in activity brought about by the administration of different pharmacological agents are affected differently by reserpine (Tripod, Bein and Meier, 1954). In view of reserpine's behavior both in the autonomic and in the somatic system, the supposition seems justified that it exerts an effect on such regulatory integrating systems.

If the assumption is generally valid that one component of the mechanism of action of reserpine depends on an activation of inhibitory mechanisms outside the carotid-sinus reflexes, the likelihood that these mechanisms are bulbar would be small. There is more probability that, in the main, they would be situated rostrally.

Summary

(1) The pharmacological characteristics of reserpine and its effects upon selected central mechanisms are described, and a comparative analysis is carried out between individual groups of symptoms produced by reserpine and by typical substances of known pharmacological effect.

(2) It is typical of reserpine that only selected and defined functional systems, both within the autonomic and the somatic system, are susceptible to its action.

(3) The analysis of defined actions of reserpine is illustrated by two examples: the inhibition of certain reflexes emanating from the carotid sinus, and the effect exerted upon certain reflexes of the respiration.

(4) Inhibition of these reflexes is dependent on a central mechanism.

(5) Section of the brain stem immediately caudal to the quadrigeminal bodies partly nullifies the action of reserpine. When the brain stem is severed,

much higher doses of reserpine are needed to inhibit the pressor reflex of the carotid sinus than with the brain stem intact.

(6) Only some of the reflexes in the respiratory sphere are affected: vagal respiratory reflexes and the sensitivity of the medullary substrates linked with them are not affected by reserpine, while chemoreflector respiratory effects are. That reserpine acts only upon defined and selected substrates can be particularly strikingly illustrated by its action upon the respiration.

(7) The extent to which differential actions upon various sympathetic substrates may be assumed within the sympathetic system is discussed. It is deduced from the example of the pressor-reflex inhibition of the carotid sinus that reserpine might activate inhibiting central substrates which, in the main, probably lie rostral of the caudal colliculi. Reserpine may be assumed to act upon central regulatory mechanisms which integrate autonomic and somatic functions.

Acknowledgments

I wish to acknowledge my sincere thanks to H. Helmich and K. Muchenberger for their skillful and valuable technical aid.

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NEUROPHARMACOLOGICAL ASPECTS OF RESERPINE

By Jurg A. Schneider, A. J. Plummer, A. E. Earl, and R. Gaunt
The Research Department, Ciba Pharmaceutical Products, Inc , Summit, N. J.

The mode of action of reserpine (Serpasil) has been under intensive investigation since Müller, Schlittler and Bein[1] identified this crystalline alkaloid from the crude extract of *Rauwolfia serpentina* Benth. When it was recognized as an alkaloid principally responsible for the pharmacological action of the whole root (Bein[2]), clinical trials were started immediately both in the field of hypertension (*e.g.* Wilkins,[3] Loeffler[4]) and psychiatric disorders (*e.g.* Sainz,[5] Noce,[6] Kline[7]). Meanwhile, the pharmacology of the new alkaloid was carefully analyzed by various groups of investigators. The general pharmacology has been discussed by Bein *et al.*[8] and Plummer *et al.*[9, 10] Tripod and Meier,[11] Trapold, Plummer, and Yonkman,[12, 13] and Cronheim *et al.*[14] analyzed some cardiovascular aspects of reserpine, whereas Tripod, Bein, and Meier[15] and Schneider and Earl[16, 17, 18] characterized the tranquilizing properties of reserpine and compared its effects with sedation obtained after administration of commonly used sedatives, especially the barbiturates. Recently, Gaunt *et al.*[19, 20] and Gross *et al.*[21] were able to give experimental evidence of the hypotensive and life-prolonging effect of reserpine in chronically induced hypertension in rats.

Reserpine is not the only pharmacologically active alkaloid found in different *Rauwolfia* species. Klohs *et al.*[22] isolated rescinnamine from *Rauwolfia serpentina* Benth. This compound was demonstrated, by Cronheim and his co-workers,[23] to have similar pharmacological effects to reserpine, although, in some respects, it seemed to be weaker (Haack,[24] Plummer[25]). The most recent development in the field of new reserpinelike alkaloids was the isolation of desmethoxyreserpine (deserpidine) from *Rauwolfi canescens* by Schlittler and his associates.[26, 27] The pharmacological activity of deserpidine lies in the same range as that of reserpine (Schneider *et al.*[28])

The general concept of the mode of action of reserpine was originally proposed by Bein.[2] According to this theory the signs of parasympathetic predominance such as miosis, hypothermia, hypotension, bradycardia, increase in gastrointestinal activity, and general inactivation or tranquilization are presumed to be caused by a reduction of activity of the sympathetic regulating centers. A further investigation of this central sympathetic depression was performed by Schneider,[29, 30] who demonstrated that the blood pressure rise after electrical stimulation of central sympathetic substrates in the hypothalamic area was not antagonized by reserpine, while vascular reflexes such as the carotid occlusion reflex were blocked. According to these results, the central sympathetic depressant effect of reserpine seemed not to be due to a direct depression of central sympathetic structures but rather to a blockade or inhibition of afferent impulses which activate these centers under normal conditions.

Although the main effects of reserpine seemed to be restricted to autonomic functions, it soon was apparent that other parts of the central nervous system were also affected by reserpine. Himwich and Rinaldi[31] were the first investigators to point out that reserpine had a stimulating effect on the reticular formation in the brain stem. These findings provided some explanation as to why animals, even under high doses of reserpine, could be aroused easily from their state of tranquilization, a condition which could be distinguished electroencephalographically from sleep induced by barbiturates (Schneider and Earl[16, 18]). Furthermore, clinical reports indicated that patients under prolonged treatment with large doses of reserpine showed signs of Parkinson's disease (Weber,[32] Barsa and Kline[33]), which also suggests involvement of functions not directly related to the autonomic nervous system. In addition, Barsa and Kline[33] observed that the convulsive threshold in electroshock therapy seemed to be lowered after reserpine. This change was demonstrated experimentally by Chen *et al.*[34] in studies in mice. These findings indicated that reserpine might have a far more general influence on the central nervous system than originally assumed. The logical place to start further investigation of this problem was the synapses in the central nervous system.

Bein (see Weber[32]) had previously investigated the effect of reserpine on spinal reflex arcs and found that no effect could be obtained in doses which normally produce symptoms characteristic of reserpine activity. The clinical and pharmacological data that had become available, meantime, prompted us to reinvestigate the problem with much higher doses of reserpine for the following reasons: It had become obvious from the studies mentioned above, that most of the drug effects which could not necessarily be attributed to the autonomic nervous system became evident only after prolonged administration of high doses of reserpine.[32, 33] The higher the doses given, the sooner these effects seemed to appear. The fact that a time/dose relationship is involved can be nicely demonstrated in a test recently published by Earl,[35] who found that emesis could be induced in pigeons given reserpine ($ED_{50} = 85\ \mu g./kg.$ subcutaneously). Using results from 240 pigeons given reserpine at six different dose levels we could demonstrate that, with increasing doses of reserpine there was not only an increased percentage of emesis, but also a reduction of time after administration at which emesis occurred. This relationship is shown in a three dimensional graph in FIGURE 1. The triangles indicate the failures in vomiting at different dose levels, showing clearly that the average time of onset of vomiting was shortened as the dose injected and the percentage of emesis was increased. This is of particular interest if a drug like reserpine has to be tested in acute preparations where clear-cut changes are imperative within as short a period of time as possible.

For these reasons the effect of doses of 5 mg./kg. intravenously of reserpine on synaptic transmission in the spinal cord was reinvestigated. In most experiments, reserpine (Serpasil) was used in its commercially available form, namely dissolved in a benzyl alcohol, citric acid, polyethylene glycol and water mixture. This mixture, later referred to as vehicle *C*, allowed a concentration of 2.5 mg./ml. In all experiments vehicle controls were done either in the same animal or in a different animal under analogous conditions.

In a few preliminary experiments, the spinal cord of cats was severed at the C_1 level under ether anesthesia, after which artificial respiration was induced.

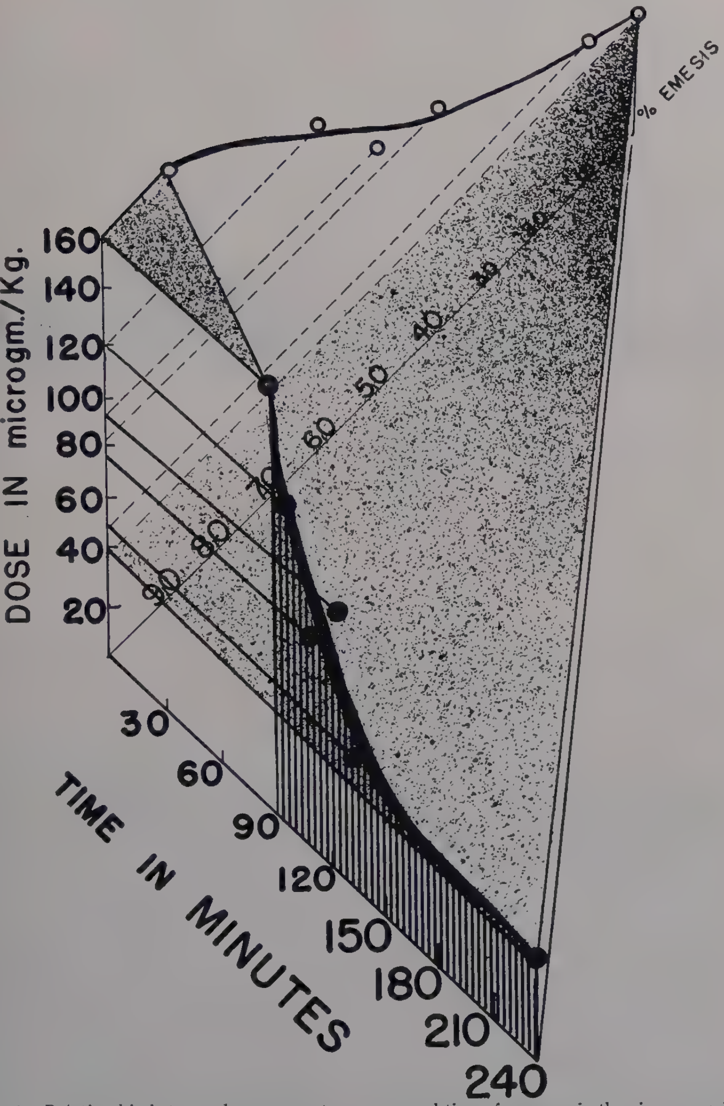

Figure 1. Relationship between dose, per cent response, and time of response in the pigeon emesis test for reserpine. Results using 6-dose levels with 40 birds per dose, plotted in a 3-dimensional graph. Ordinate: dose injected i.m. Front abscissa: average time of onset of emesis in minutes. Rear abscissa: per cent of birds showing emesis. As the dose is increased, the percentage of emesis increases. Simultaneously the average time between drug injection and onset of emesis is shortened. This decrease is indicated by vertical bars. The triangles are representations of the failure to show emesis, which is considerably reduced at higher doses. The graph shows that very high single doses of reserpine may have to be given in acute experiments in order to obtain clear-cut results in a reasonable period of time.

The knee jerk in these animals was tested by means of a hammer which hit the patellar region once every 15 seconds. The lower portion of the corresponding hindleg was connected to a lever, which in turn recorded the excursions on a smoked drum. The animal was allowed to recover from ether anesthesia for at least one hour before any drug was injected.

In this preparation, a clear-cut facilitation of the knee jerk could be observed after reserpine, whereas the vehicle was without effect (FIGURE 2). Such facilitation might be mediated at either of two sites: The synapses in the spinal cord or the effector organ. The following test was used to detect the possible effects

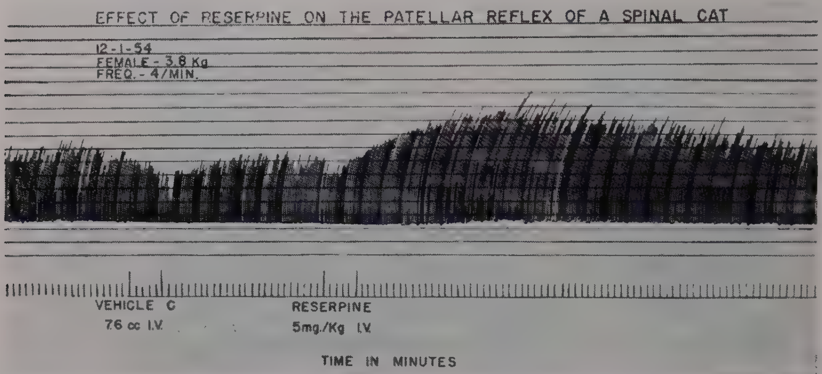

FIGURE 2. Demonstration of the facilitation of the knee jerk by reserpine. Note the gradual increase in height of contraction which reaches its maximum 20 to 30 minutes after onset of the injection.

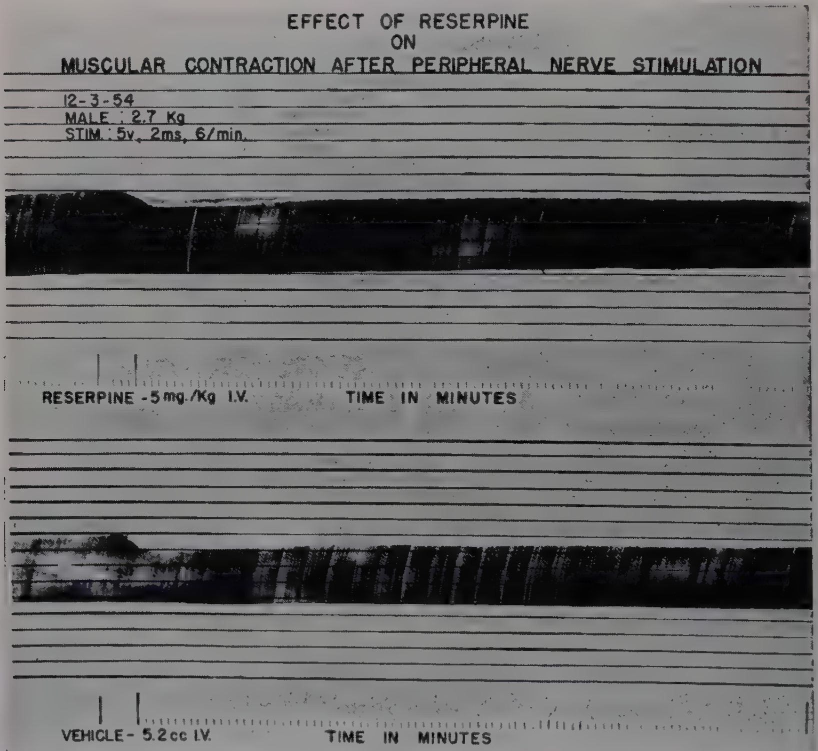

FIGURE 3. The muscular contraction after peripheral nerve stimulation is reduced both by reserpine in vehicle *C* and vehicle *C* alone. An effect of reserpine on the muscle or the myoneural junction cannot be demonstrated at the doses employed.

of high doses of reserpine on the myoneural junction itself. Spinal chords of cats were severed as described and periodical stimulation was applied to the centrally-cut peroneal nerve. The resulting contraction of the tibialis anterior muscle was recorded. Both reserpine in vehicle *C* as well as vehicle *C* alone, caused a reduction in the height of contraction of the muscle (FIGURE 3) thus indicating that the facilitation of the knee jerk was central in origin. These results indicated the need for an electrophysiological study of the possible effects of reserpine on spinal synapses. Cats were decerebrated under ether anesthesia, and artificial respiration was started in order to combat the respiratory depression or paralysis which reserpine may induce in decerebrated animals. The spinal cord was exposed, and dorsal and ventral roots, usually of the S_1 segment were prepared according to the technique of Brooks *et al.*[36] Square wave impulses from a Grass stimulator were used to stimulate dorsal roots, whereas the resultant action potentials were picked up from ventral roots with platinum electrodes and fed into a DC amplifying system. Records were taken with a Grass camera from a DuMont dual beam cathode-ray oscilloscope.

The familiar shape of ventral root potentials after dorsal root stimulation is shown in FIGURE 4. As first demonstrated by Lloyd and his co-workers,[37] the first spike after the stimulus artifact represents the impulse passing through a monsynaptic reflex arc. It is followed by a series of smaller spikes which represent polysynaptic pathways.

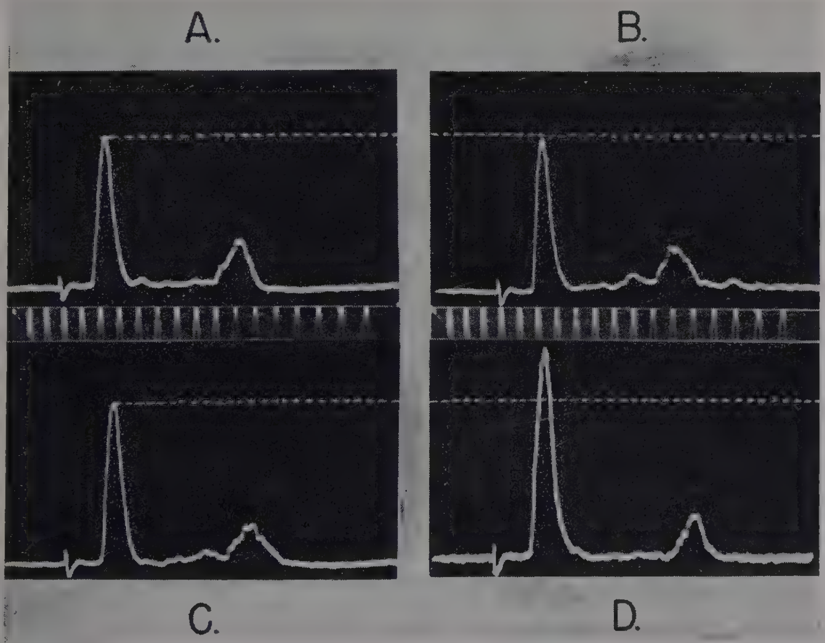

FIGURE 4. Action potentials recorded from ventral roots of the spinal cord after dorsal root stimulation in the cat. The large spike following the stimulus artifact is the monosynaptic potential, whereas the smaller and less defined deflection represents the polysynaptic potential. Time in milliseconds. *A:* control. *B:* 30 minutes after i.v. injection of vehicle *C*. *C:* Control. *D:* 60 minutes after i.v. injection of reserpine, 5 mg./kg. Note the clear-cut increase in height of the monosynaptic spike.

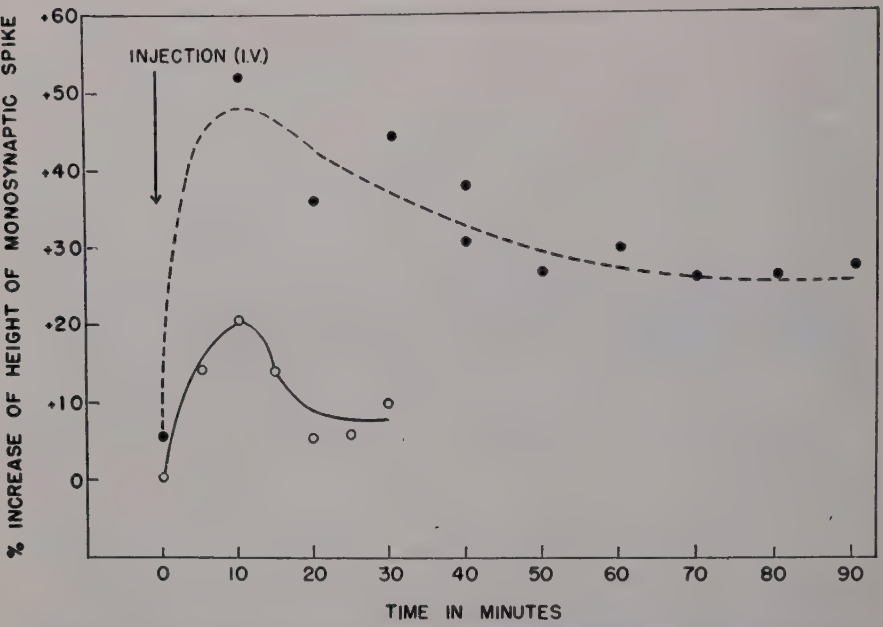

FIGURE 5. Graphical reproduction of the height of monosynaptic potentials evoked by dorsal root stimulation in the cat. Rings and uninterrupted line: values obtained after injection of vehicle *C*. Average of two experiments. Dots and interrupted line: values obtained after injection of reserpine 5 mg./kg. Average of three experiments.

Doses of 5 mg./kg. of reserpine in vehicle *C* definitely increased the height of the monosynaptic spike (FIGURE 4D, FIGURE 5). This increase could be followed over a period of hours.

Vehicle *C* alone produced a transient increase in the monosynaptic spike (FIGURE 5), which, however, returned to normal after 20 to 30 minutes (FIGURE 4B).

Whether the polysynaptic spikes were significantly increased cannot be decided as yet. In some experiments, this seemed to be the case but, in others, the results were equivocal. No decrease could be obtained, however, as is typical for Myanesin (Berger *et al.*,[38] Henneman *et al.*,[39]) or for 0-methoxyphenylglycerol ether (Schneider and Earl[40]).

Synapses on the afferent side of the somatic nervous system were not tested directly. There is indirect evidence, however, that reserpine does not have any blocking effect on these synapses. Thus the reaction time to pain stimuli in mice is not altered by reserpine (Bein *et al.*,[2] Schneider[41]). Reserpine apparently did not influence single unit impulses from the sensory areas of the cat cortex evoked by touch stimuli, a finding which is in accord with the results obtained in the analgesia tests in mice. Whether the antagonism of reserpine against the analgetic effect of high doses of morphine (Schneider[41]) or its antagonism toward the anticonvulsive effects of dilantin (Chen[34]) are related to the facilitatory effects of reserpine on synaptic transmission is yet to be decided.

It should be kept in mind that the facilitatory effect of reserpine on synaptic transmission can be demonstrated only after very high single doses of the drug.

Nevertheless, this effect may well be an important clue to the nature of the basic mechanism of the action of reserpine. The clinical observations of Parkinsonian symptoms (Weber,[32] Barsa and Kline[33]) and the lowering of the convulsive threshold[33] certainly indicate that other than central autonomic effects can be obtained after clinical doses of reserpine. The results of our studies reinforce these suggestions that the effect of reserpine is probably far more generalized than originally assumed.

The question arises immediately how such findings can be correlated with other pharmacological facts and the present theory of reserpine activity. Bein's original postulation of a central sympathetic blocking effect of reserpine[2] gave a satisfactory explanation for most of the effects of reserpine which concerned the autonomic nervous system. The new findings on facilitation of transmission in central synapses may possibly throw some light on the nature of this mechanism.

In an attempt to correlate all existing information we have tried to develop below a more comprehensive working hypothesis, one which is admittedly still highly speculative (FIGURE 6).

From the basic work of Bard[42] and of Cannon and Britton[43] it is generally known that removal of the cerebral cortex causes a state of sham rage which is characterized by general excitement of the animal, hyperexcitability, pupil dilatation, contraction of the nictitating membrane, tachycardia, increase in blood pressure, associated with increased vascular reflexes, panting, *etc.* According to Ranson and Magoun,[44] this phenomenon is due to the removal of the inhibitory function of the cortex on the brain stem, especially the diencephalic area. When cats in sham rage were given reserpine the rage picture was antagonized. Nevertheless, the full effect of reserpine activity could not be obtained in these decerebrated animals (Schneider[29, 30]). The presence of the cortex apparently is necessary to produce the characteristic effect of reserpine. Since the pharmacodynamic effects of reserpine are in direct contrast to the findings in sham rage as far as autonomic functions are concerned, one might postulate that reserpine causes an increase of cortical inhibition on diencephalic structures. Thus, a state of quietude, miosis, relaxation of the nictitating membrane, hypotension, bradycardia, *etc.* would have to be expected; in short, the symptoms which characterize reserpine activity. Our most recent findings on facilitatory effects of reserpine on synaptic transmission certainly would fit into this working hypothesis. Parasympathetic predominance associated with inhibition of afferent impulses would be caused by the facilitation of inhibitory cortical influences. This concept would also permit explanations for other phenomena of reserpine which are not necessarily linked to the central autonomic regulation. The central sympathetic depression would merely become part of a more general pharmacodynamic effect of reserpine which affects synaptic transmission and possibly other functions of nerve transmission. Different synapses in the central nervous system might also be affected at different dose levels.

No experiments have been done, as yet, to determine the mechanism by which reserpine augments the action potentials of synapses in the spinal cord. It would not be surprising to find the acetyl-choline mechanism involved although

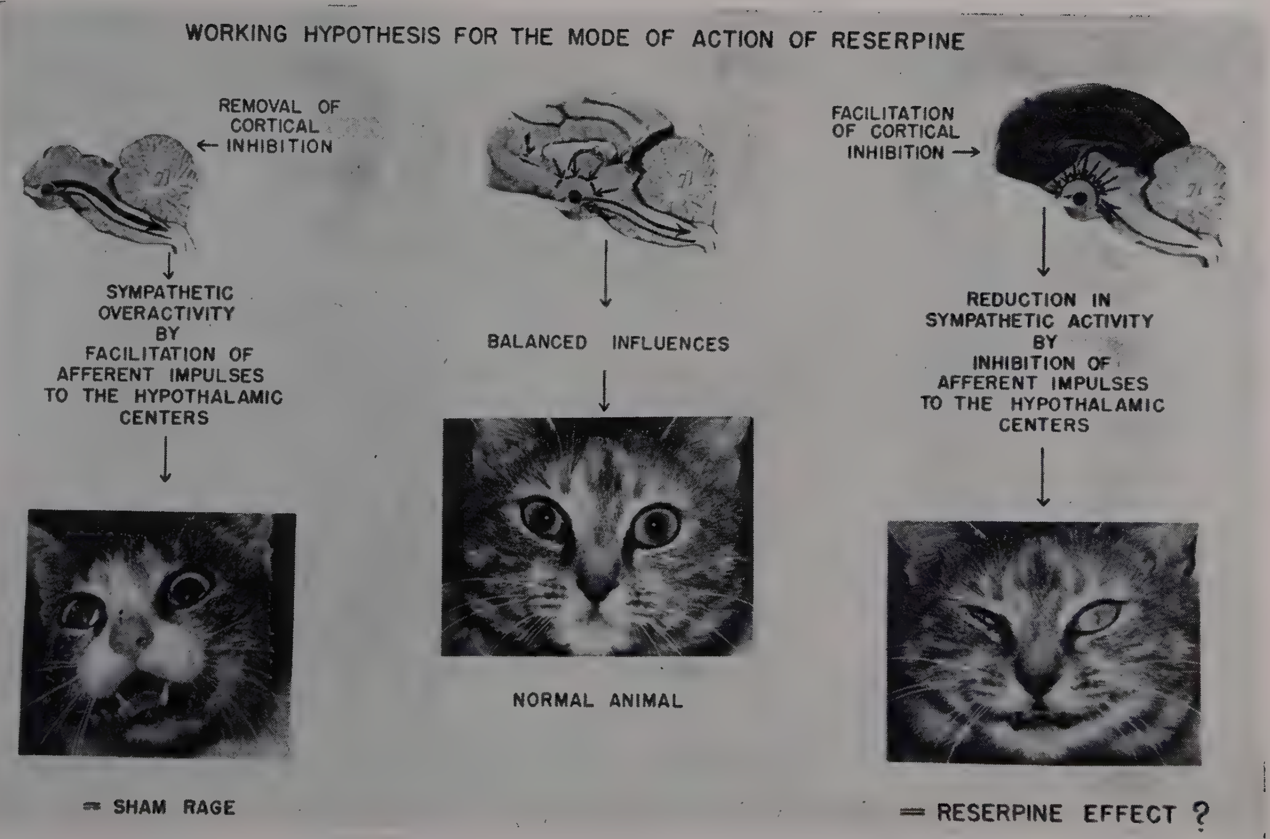
WORKING HYPOTHESIS FOR THE MODE OF ACTION OF RESERPINE
REMOVAL OF CORTICAL ← INHIBITION
SYMPATHETIC OVERACTIVITY BY FACILITATION OF AFFERENT IMPULSES TO THE HYPOTHALAMIC CENTERS
= SHAM RAGE
BALANCED INFLUENCES
NORMAL ANIMAL
FACILITATION OF CORTICAL INHIBITION →
REDUCTION IN SYMPATHETIC ACTIVITY BY INHIBITION OF AFFERENT IMPULSES TO THE HYPOTHALAMIC CENTERS
= RESERPINE EFFECT ?

FIGURE 6. Working hypothesis for the hypothalamic point of attack of reserpine.

consideration of that possibility must await appropriate biochemical study. In any case, the demonstration of a facilitatory action of reserpine on synaptic transmission suggests a new aspect to the mode of action of a drug which has proved to be of great theoretical and practical interest.

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A COMPARISON OF EFFECTS OF RESERPINE AND SOME BARBITURATES ON THE ELECTRICAL ACTIVITY OF CORTICAL AND SUBCORTICAL STRUCTURES OF THE BRAIN OF RABBITS

By Franco Rinaldi* and Harold E. Himwich
Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Galesburg, Ill.

Reserpine (Serpasil), an alkaloid from *Rauwolfia serpentina*,[1, 2] has been found useful in the management of disturbed psychotic patients.[3, 4] Unlike barbiturates, it renders patients less active without inducing sleep. This action, peculiar to reserpine, has been called a tranquilizing effect. Evidence that this state of quiescence is distinctly different from sedation induced by barbiturates is revealed by the fact that, in monkeys, reserpine does not produce an electroencephalographic picture of sleep.[5]

It has been shown that the hypnotic action of barbiturates is related to the depression that these drugs exert upon the brainstem arousal mechanism.[6] This fact inspired our work, the aim of which was to investigate further the nature of the tranquilizing effect of reserpine in its relationship with the action of this drug upon the electrical activity of the brain and the function of the mesodiencephalic activating system.

Under the unitary denomination "mesodiencephalic activating system" (MDAS), we include, for purposes of description, the reticular formation of the brainstem tegmentum of Moruzzi and Magoun[7] and the thalamic diffuse projection system of Jasper.[8] Both these structures have the property, when stimulated, of altering, in a diffuse manner, the electrical activity of the cerebral cortex, producing the so-called electrographic alerting or activating or arousal responses.

Drugs that produce widespread electrocorticographic changes that consist only of enhancement of the spontaneous sleeping characteristics or, conversely, of those of alertness, act upon the MDAS. Inhibition of the MDAS brings about a dominance of the features of sleep, whereas stimulation of the MDAS causes a predominance of the alert picture.

In the experiments reported in this paper, the actions of reserpine, pentobarbital, thiopental, and phenobarbital upon the cerebral electrical activity and upon the MDAS were studied in rabbits. The effects of reserpine and barbiturates will be compared to that of atropine, specific depressant of the MDAS.[9]

Methods

The experiments were performed in adult albino rabbits, unanesthetized, curarized, and maintained by artificial respiration.

The electrical activity of different brain structures (motor and limbic cortices, caudate nuclei, and thalamus) was recorded by means of bilaterally placed electrodes, according to a technique elsewhere described.[9] For the recording, an eight-channel, ink-writing electroencephalographic instrument (Grass D No. 3) was used. In most experiments, the electrocardiogram was also obtained. Another electrode (bipolar, coaxial, of stainless steel, insulated except for the tip, with a distance of 2 mm. between the two bare ends) was placed with its tip located in the midbrain reticular substance at the level of the anterior quadrigeminal body.

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* Fulbright Fellow, on leave from the Clinic for the Diseases of Nervous System of the University of Cagliari, Cagliari, Italy.

The location of all subcortical electrodes was checked by means of serial sections of formalin-fixed, paraffin-embedded whole brains, using the staining technique of Klüver and Barrera.[10]

In order to evoke electrographic alerting responses, several techniques were used in all animals: auditory stimuli (clapping of the hands), tactile stimuli (touching the fur of the forepaws), pain stimuli (twisting the digital joints or pinching the skin), and direct electrical stimulation of the midbrain reticular formation (direct current square pulses; frequency 250–300 c/s; duration of pulses, 2 milliseconds; length of stimulation, 0.5–3 seconds; voltage, 1–9 volts; the stimulating current was provided by a Grass stimulator, Model S-4 in connection with an isolation unit). Another technique used to evoke the alerting electrographic response was the intracarotid injection of 0.5 to 15 micrograms of acetylcholine with a procedure previously described.[9]

The drugs employed in this study were: reserpine (Serpasil),* pentobarbital sodium (Nembutal), thiopental sodium (Pentothal), phenobarbital sodium, atropine sulfate, and acetylcholine chloride. Di-isopropylfluorophosphate (DFP), a powerful anticholinesterase agent, was also occasionally employed because of its property of producing a long-lasting stimulation of the MDAS that results in a continuous pattern of alertness.[9]

Results

1. *The normal cerebral electrographic patterns of the curarized unanesthetized rabbit.* The cerebral electrical activity of the curarized unanesthetized rabbit shows two main patterns that are remarkably similar in all animals and well defined in their features, provided that curarization is maintained at a constant level and the conditions of artificial respiration carefully regulated.[9]

The first pattern (FIGURE 1, left half) is present when the animal is left undisturbed. We shall call this pattern the resting or sleep pattern. It is characterized by high voltage (100 to 300 microvolts) slow (1 to 3 c/s) waves and spindles of 14 c/s waves. This type of activity continues unbroken until some accidentally or purposefully induced stimulus (auditory, tactile, painful, *etc.*) disrupts it and brings forth, instead, the second pattern. The latter pattern (FIGURE 1, right half) that we shall call the alert pattern, is characterized by (a) the elimination of all slow waves and spindles; (b) the appearance of a very regular 4 to 7 c/s rhythm of medium amplitude, clearly of thalamic origin; (c) the presence, mainly in the motor cortex of low-voltage fast rhythms. The onset of the alert pattern is abrupt, and its duration varies with the intensity and the type of the stimulus. Of the physiological stimuli, pain is the most

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* The reserpine (Serpasil) used in this study was provided by Ciba Pharmaceutical Products, Inc., Summit, N. J.

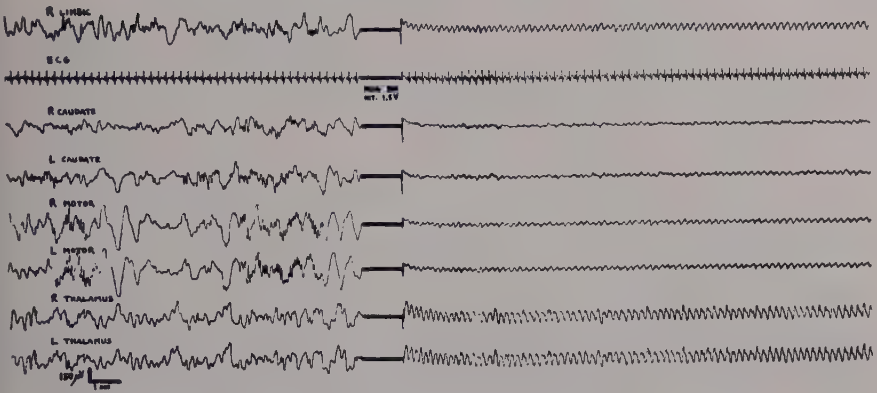

FIGURE 1. Cerebral electrical activity of the curarized unanesthetized rabbit. The leads are (from the top tracing to the bottom one): (1) right limbic cortex, (2) EKG, (3) right caudate nucleus, (4) left caudate nucleus, (5) right motor cortex, (6) left motor cortex, (7) right thalamus, (8) left thalamus (See description in the text).

efficacious. But the strongest response is obtained with direct electrical stimulation of the midbrain reticular formation.

Intracarotid acetylcholine, in minute amounts, also produces an alerting response similar to that evoked by other stimuli. DFP introduces a long-lasting pattern of alertness, while atropine paralyzes the alerting mechanism to the point that, even with electrical stimulation of the midbrain reticular formation, it is not possible to elicit an alert pattern. The reason for these opposite effects of cholinergic and anticholinergic drugs is that a cholinergic mechanism is involved in the function of the mesodiencephalic activating system.[11]

(2) *The effects of reserpine.* Reserpine was administered intravenously in repeated single doses of 0.05 to 0.5 mg./kg., at intervals of 20 to 30 minutes. The total amount of drug per animal varied between 0.5 to 3 mg./kg. Up to 0.5 mg./kg. no change of the electrical activity of the brain was observed. The alerting mechanism was not depressed, since even a very light sound stimulus produced an alerting response. Bradycardia and myosis were already clearly present after administration of 0.5 mg./kg. of reserpine.

As the dosage was increased gradually to 1 mg./kg., the cerebral electrographic picture began to change. Alerting responses to accidental stimuli occurred more often; their duration was longer lasting; the threshold for electrical stimulation of the midbrain reticular formation was definitely lowered. Larger amounts of reserpine (1.5 mg./kg. to 2.0 mg./kg.) finally caused the persistent presence of an electrographic picture of alertness with complete absence of the characteristics of sleep, such as the high-voltage slow waves and the 14 c/s spindles (FIGURE 2). It is to be noticed that the effects of reserpine on the cerebral electrical activity always appeared after a latency of 20 to 30 minutes, following the injection of an adequate dose.

The electrographic pattern of alertness, continuously present after reserpine, was not distinguishable from the spontaneous one in any feature, except per-

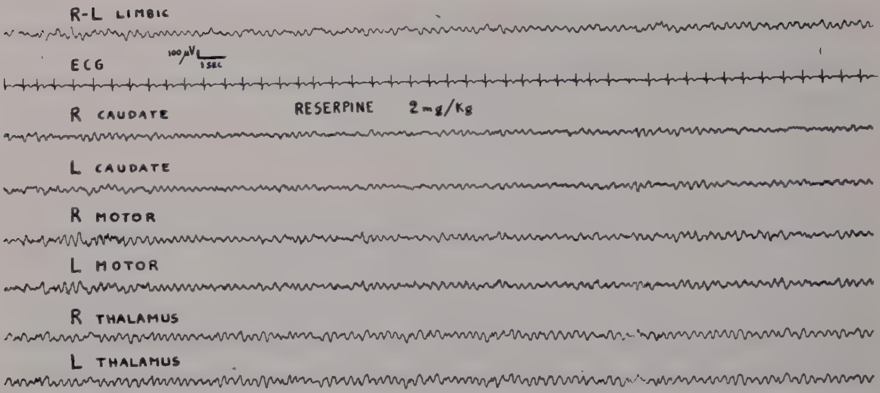

FIGURE 2. Cerebral electrical activity of the rabbit after the administration of 2 mg./kg. of reserpine. Leads as in FIGURE 1. Note the resemblance of this picture to the normal alert pattern (FIGURE 1, right half) mainly in the absence of sleep spindles and of high voltage slow activity and in the presence of four c/s thalamic rhythm. Note also the bradycardia induced by reserpine.

haps for the frequency of the thalamic rhythm that tended to be at the lower limit of its usual range of variation; *i.e.*, 4 to 5 c/s instead of 4 to 7 c/s.

(3) *The effects of barbiturates.* We administered various barbiturates, slow-acting ones such as phenobarbital [in doses from 10 to 100 mg./kg. intraperitoneally (i.p.)], and more rapid examples, as pentobarbital (10–60 mg./kg. i.p.) and thiopental (10–40 mg./kg. intravenously (i.v.) at a rate of 4 mg./kg. per minute).

The well-known progressive effect of barbiturates was observed.[12, 13, 14, 15, 16, 17, 18, 19] The electrographic characteristics of sleep became more and more prominent. The known stages of progressive depression were observed to appear in more or less rapid succession according to the type of barbiturate used.

(a) At first the 14 c/s spindles increased in amplitude and occurred at shorter intervals. The high-voltage slow waves were also augmented in amplitude. Slow waves and spindles that are more prominent in the motor cortex during spontaneous sleep appeared with progressively greater amplitude, also in the thalamus and in the caudate nucleus, so that there was less apparent difference between cortical and subcortical tracings.

(b) In deeper narcosis or depression, the spindles occurred less frequently and the 14 c/s waves, of which the spindles are made, became sharper, almost spikelike, and often less biphasic in character. Some of them appeared as monophasic points. Moreover the frequency of the spindles dropped from the usual 14 c/s to 12 and also 10 c/s. The slower (1 to 3 c/s) waves became diffusely predominant and changed somewhat in form. Their positive deflection became sharper, pointlike, while the negative deflection maintained more or less a rounded form.

(c) At a still deeper stage of narcosis, blackouts appeared: periods of 2 to 3 seconds of almost complete electrical inactivity interrupted by bursts of slow waves.

(d) Finally a stage was reached when the cortex was practically silent, though some slow activity was still seen in subcortical records.

At different stages of barbiturate narcosis, we studied the effects of various

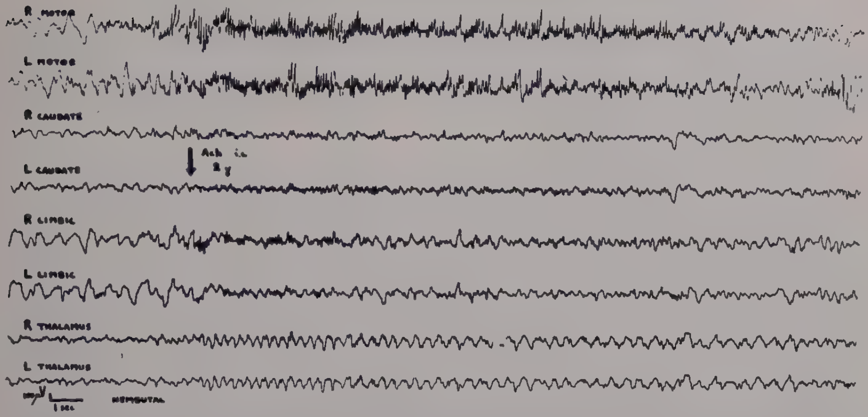

FIGURE 3. A cerebral electrographic alerting response to the intracarotid injection of two gamma of Ach in a rabbit in nembutal (40 mg./kg.) narcosis. The leads are (from the top tracing to the bottom one): (1) right motor cortex, (2) left motor cortex, (3) right caudate nucleus, (4) left caudate nucleus, (5) right limbic cortex, (6) left limbic cortex, (7) right thalamus, (8) left thalamus. Notice that the alerting response in the motor cortex consists of a high-voltage fast activity (12 to 15 c/s), while the thalamic response still resembles the normal one, a 4 c/s rhythm.

alerting stimuli. It is true that, at progressive depths of narcosis, the alerting electrographic responses are shorter in duration and require stronger stimulation. Actual block of responses, however, could not be demonstrated until an advanced stage was reached, characterized by periods of electrical inactivity. Despite deep sleep, when short blackouts were present, electrical stimulation of the midbrain reticular formation, intracarotid acetylcholine and, often, a strong pain induced a clear alerting response (FIGURE 3).

It is important to note that this alert pattern under barbiturates is peculiar and different from the normal one. The slow waves and spindles are interrupted. In the thalamus, a 4 to 5 c/s rhythm is evoked not very different from the normal, but in the motor cortex (and in the caudate nucleus) the usual fast low-voltage activity does not appear but, instead, a high voltage 14 to 18 c/s activity (in lighter narcosis a little faster 18 to 22 c/s).

This peculiar cortical high-voltage fast activity is a typical barbiturate effect. It appears in the cortex as a response to an alerting stimulus, even under the action of small doses of barbiturates, when the threshold of the midbrain reticular formation to electrical stimulation is not yet significantly depressed and the thalamic response remains normal. The cortical fast activity often described by many authors as the first stage of barbiturate narcosis, appeared to be, in our preparations, identical with the above-mentioned high-voltage, fast alerting response.

Another important observation is that, in deeper stages of narcosis, an alerting stimulus may be insufficient to evoke a cortical diffuse response. Only the thalamic one is observed.

Discussion

The effects of reserpine on the electrical activity of the brain of the rabbit and on the MDAS are unequivocal and unidirectional. In relatively low doses (up to 0.5 mg./kg.), no changes are detectable. In relatively large doses (1 to 2 mg./kg.), reserpine induces a continuous pattern of alertness and stimulates rather than depresses the MDAS.

Barbiturates, quite differently, enforce the electrographic characteristics of sleep and depress the MDAS.

It is easy to conclude that reserpine has nothing in common with hypnotic drugs such as the barbiturates, so far as changes of the electrical activity of the brain and of the function of the MDAS are concerned. This may explain the lack of hypnotic action among the effects of reserpine despite its tranquilizing power. But our results yield additional data and evoke several questions. According to the most widely accepted opinion, there is concordance between the level of activity of the MDAS and the production of sleep.[20] A hyperactive MDAS calls for behavioral alertness as well as for electrographic alertness. A depressed MDAS, on the contrary, calls for sleep and for electrographic signs of sleep. If this were the entire picture one would expect reserpine, which stimulates the MDAS and produces a definite electrographic pattern of alertness, to be not only a nonhypnotic drug but to produce insomnia. Such a conclusion is not true, particularly in the rabbit. In fact, in the rabbit, reserpine, far from producing insomnia, acts as a behavioral sedative in doses between 0.1 and 50.0 mg./kg., a range which includes and goes beyond the amounts employed in our experiments to excite the MDAS.

Additional data on the pharmacology of the MDAS, as well as our results on the effects of barbiturates, will help us elucidate the above-mentioned dilemma.

(1) Reserpine produces overactivity of the MDAS and an alert pattern of brain electrical activity, but not insomnia.

(2) Atropine paralyzes the MDAS but is not a hypnotic. In our previous work,[9] we observed that 10 to 15 mg./kg. of atropine completely paralyzed the alerting mechanism to the point that, even with electrical stimulation of the midbrain reticular formation, it was not possible to elicit an alerting electrical response. Despite this fact, the animal with such a dose of atropine does not appear to be narcotized; not even sleepy, but practically normal.

(3) Barbiturates, typical hypnotic compounds, are indeed depressants of the MDAS, but one must give doses large enough to produce almost total cortical eclipse, a prelethal depression, before a paralysis of the MDAS comparable to that one obtained with atropine is attained.

(4) From the preceding facts, it is obvious that, while there is full concordance between the functional status of the MDAS and the electrical brain activity (overactive MDAS corresponding to an alert EEG pattern, depressed MDAS in accordance with the sleep features in the EEG picture), there is not such agreement between the function of the MDAS and the physiological status of sleep or alertness. The quiescence of the MDAS is a part of sleep, but it also occurs in the absence of sleep. *Per contra*, the hyperactivity of the MDAS is a part of alertness but its presence does not necessarily call for insomnia. Therefore, one must not be surprised to find that reserpine does not produce insomnia.

But this same reasoning obviously weakens our former deduction that the overactivity of MDAS justifies the lack of hypnotic action for reserpine. Additional light is shed on this question by examining the action of barbiturates. This group of drugs produces changes of the cerebral electrical activity that differ basically from a simple enforcement of the sleep patterns and the related depression of the MDAS.

These changes are:

(1) Modification of the type of response of the cerebral cortex to alerting stimuli (introduction of a high-voltage fast type of response). This is an early change seen also with small doses. It is not present with atropine, which simply shortens the response if the dose is not sufficient to paralyze the MDAS.

(2) While the cortical-electrical response to an alerting stimulus is modified early, the thalamic reaction still largely retains its normal features (4 to 6 c/s rhythm).

(3) The diffuse alerting response in the cortex is lost before the thalamic one.

Thus a special effect exerted predominantly on the cortex may account for part of the hypnotic action of barbiturates. Not only is the barbiturate depression selective for certain nuclear areas, but it also reveals a progressive march down the neuraxis, starting from the cephalad structures and extending in a caudad direction toward the medulla.[21] The more profound depression of barbiturates upon the cerebral cortex and caudate nuclei, in contrast to a lesser effect on the thalamus, is therefore in accordance with part of their complex pattern of action.

The above-mentioned changes induced by barbiturates offer another point of difference with regard to reserpine: not only does reserpine induce an alert pattern but that pattern is not different from the normal. There are no changes of cortical response of the type induced by barbiturates.

Our conclusion is that reserpine cannot be considered a hypnotic drug when its effects on the cerebral electrical activity are compared with those of barbiturates, for the following reasons: (1) reserpine induces an alert EEG pattern, barbiturates induce a pattern of sleep; (2) reserpine stimulates the MDAS, barbiturates depress the MDAS; (3) the cortical electrical response to alerting stimuli under reserpine is normal in type, the cortical electrical response under barbiturates reveals abnormal characteristics; (4) reserpine is not a hypnotic drug because, within the same range of dosage within which it reduces spontaneous activity and depresses certain parts of the brain—for example, the hypothalamus[21]—it stimulates the activating system and evokes the alert electrographic picture.

The fact that reserpine stimulates the activating mechanism, which includes the brainstem reticular formation, may offer a clinically important explanation of a side effect of reserpine. It has been observed that a number of patients treated with reserpine develop Parkinsonlike symptoms.

In recent years, experimental evidence has been produced[23, 24, 25, 26] that the brainstem reticular formation plays an important role in the genesis of the extrapyramidal symptoms of the Parkinson disease. The stimulation of the reticular formation[25, 26] produces a rhythmically alternating tremor. This tremor is abolished by atropine. On the other hand, atropine, and also the synthetic drugs that are most useful in the treatment of the Parkinson syndrome, are the most powerful depressants of the reticular formation. A similar correlation has been shown in regard to the effect of the cerebral electrical activity following stimulation of the midbrain reticular formation.[27] The best anti-Parkinson drugs are the most powerful inhibitors of the electrographic alerting reaction. In this respect, reserpine, which stimulates the activating system, acts upon the reticular formation in a way opposite to that of atropine. This effect on the activating system is probably the reason why reserpine may produce a Parkinsonlike symptomology as a side effect.

Summary and Conclusions

After comparing the actions of reserpine and of various barbiturates on the electrical activity of different parts of the rabbit brain, with particular regard to the effect of those drugs upon the mesodiencephalic alerting system, we draw the following conclusions: (1) reserpine produces an alert electroencephalographic pattern; (2) barbiturates induce a pattern of sleep; (3) reserpine stimulates the mesodiencephalic activating system; (4) barbiturates depress the mesodiencephalic activating system; (5) under reserpine, the cortical electrical response is normal in type; (6) with barbiturates the cortical electrical response to the same stimuli reveals abnormal characteristics; (7) reserpine cannot be considered a hypnotic drug when its effects on the cerebral electrical activity are compared to those of barbiturates; and (8) the fact that reserpine stimulates the activating system and evokes the alert electrographic pattern explains why reserpine does not enforce sleep.

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THE EFFECTS OF RESERPINE ON EMOTIONAL BEHAVIOR OF NORMAL AND BRAIN-OPERATED MONKEYS

By Lawrence Weiskrantz and William A. Wilson, Jr.
Department of Neurophysiology, The Institute of Living, Hartford, Conn.

The untamed rhesus monkey appears to be affected in much the same way by reserpine as it is by certain brain lesions. In its normal, untreated state, a monkey will invariably withdraw from human observers, usually grimacing or screeching loudly, will frequently attack if cornered, and cannot be petted unless actually physically restrained.

The following descriptions would never be applied to normal animals:

" . . . the monkey can now be handled with little fear that he will strongly resist any manipulation to which he is submitted" (Earl, 1953).

"The physical and emotional response to a threatening situation was markedly reduced and the approach of another animal or human, which ordinarily would have evoked a defiant attack or prompt flight, was now amiably tolerated" (Plummer *et al.*, 1954).

" . . . animals were markedly altered in their behavior with respect to man, permitting petting and handling without any visible excitement, or even approaching and reaching for observers" (Weiskrantz, 1953).

" . . . the authors independently felt it safe to enter the animal's cage and 'petted him for a considerable time.' When the observer placed his hand in the animal's mouth, it was chewed very gently" (Pribram & Bagshaw, 1953).

The first two statements refer to animals treated with reserpine; the last two refer to monkeys who had been subjected to bilateral lesions in the anterior medial portion of the temporal lobes, including the amygdaloid complex and prepyriform cortex. Other similarities can be pointed out, among them an increase in gastrointestinal activity (Plummer *et al.*, 1954; Wilson, 1954), a decrease in rectal temperature (Plummer *et al.*, 1954; Pribram and Bagshaw, 1953), and awkwardness of posture (Plummer *et al.*, 1954; Weiskrantz, 1953).

The present report is an account of an attempt to compare directly the effects of these two independent variables—the lesion and the drug, as well as to investigate whether the effect of reserpine is altered in an animal who has sustained an amygdala lesion. Since one of the most striking changes in gross behavior produced by either variable seems to be the tolerance of situations and stimuli which normally are strongly aversive, it was decided to study the behavior in a situation in which the aversiveness, or "punishing" strength of a stimulus could be carefully controlled. For this purpose, we used a variant of a situation first described by Sidman (Sidman, 1953) which, in addition to providing a quantitative measure of the animal's performance, permitted us to obtain a specification of how strong an electric shock was required for each animal to elicit reliable avoidance behavior.

Subjects

Seven immature rhesus monkeys (*Macaca mulatta*) were subjects. All were untamed and experimentally naive, except for brief participation in an earlier experiment involving food reward. Age range was estimated to be between one and two years. The animals were divided into Group I, with three animals, and Group II, with four animals.

Method

Apparatus. Two similar sets of apparatus were employed, Group I having been tested with one (Apparatus I) and Group II, with the other (Apparatus II). Both consisted of small cages in which a single manipulandum was available. In Apparatus I, this manipulandum was a small rectangular panel on the front wall of the cage. In Apparatus II, it was a protruding lever. Either the pushing of the panel or the depressing of the lever activated a microswitch which was connected with a recording device. Both apparatuses were soundproofed, the former by being placed within a large refrigeration room, and the latter by being placed within a small converted refrigerator. In both cases, there was a masking noise provided by air blowers. In neither instance was the refrigeration compressor unit functioning. Subjects could be seen through one-way vision windows. FIGURE 1 is a picture of an animal inside Apparatus II. For an illustration of Apparatus I, the reader is referred to an earlier study (Weiskrantz, 1953).

All experimental sessions were conducted automatically by means of relay and timer apparatus not shown in FIGURE 1. This apparatus was set up to operate according to the following contingencies: A push of the panel (or press of the lever) delayed the occurrence of a brief electric shock by 10 seconds. Regardless of when a push occurred, the next shock would not be delivered until 10 seconds after the *last* response. Hence, if an animal pushed the panel at least once every 10 seconds, he would never receive a shock. If, however, a shock was permitted to occur, the next one would occur, not 10 seconds later, but 2½ seconds later, until the animal responded once again, thereby delaying the next shock by 10 seconds. In Sidman's terminology, these contingencies consisted of a response-shock interval of 10 seconds, and a shock-shock interval of 2½ seconds. The apparatus automatically tabulated the number of responses made and the number of shocks delivered, as well as providing a cumulative graph of the animal's performance.

Shocks were delivered to the animal through a low resistance chain attached to an aluminum collar around the animal's neck. Both the chain and collar were permanently fixed to the animal. During experimental sessions, the animal's chain was attached to a beaded-chain swivel, which was connected to an insulated fixture on top of the cage. The cage itself provided one pole of the circuit. Wires supplying electrical charge were heavy-duty ignition cable.

The shock circuit is shown in FIGURE 2. The intensity of the shock could be varied by changing the variable resistor shunted across the primary coil. After preliminary work, it was decided to use six values of shock, calculated to give nearly equal increments in total electrical charge delivered to the animal. For convenience, we shall label these values from 1 to 6, 6 being the strongest value. The actual resistances corresponding to these values are ½, 1, 2, 4, 19, and 400 ohms. The only large deviation from equality of intervals occurs between shocks 5 and 6, this interval being only about one third the size of the others.

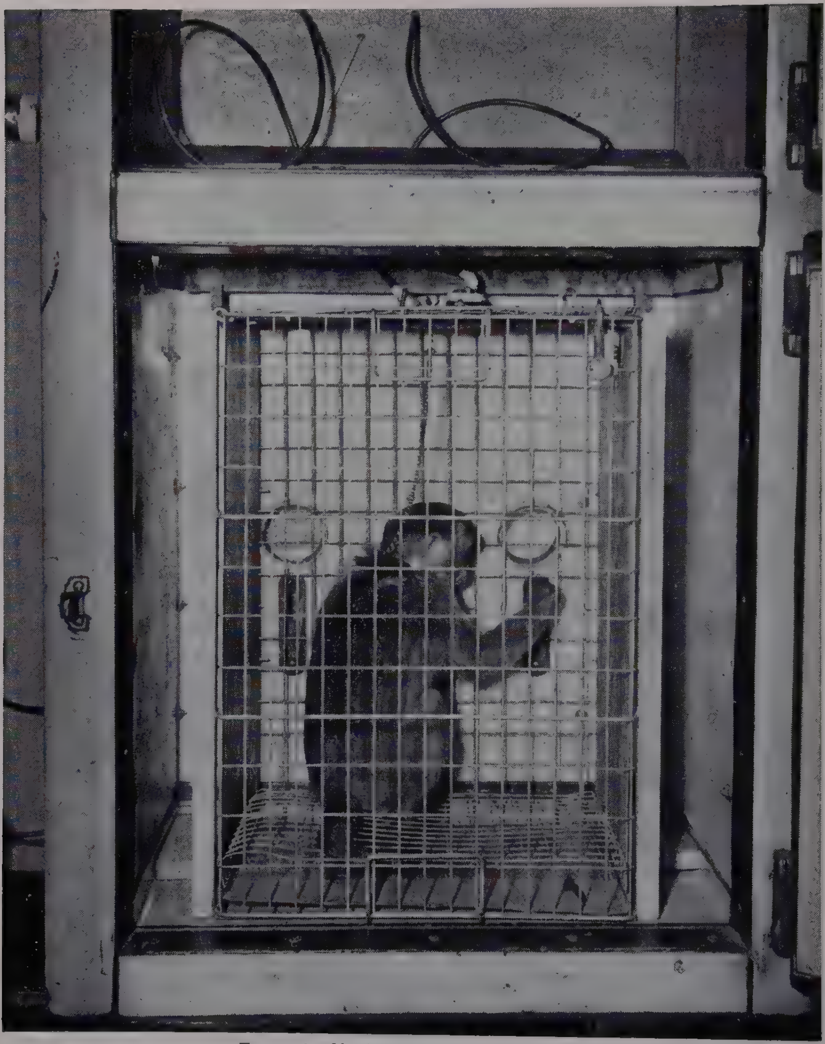
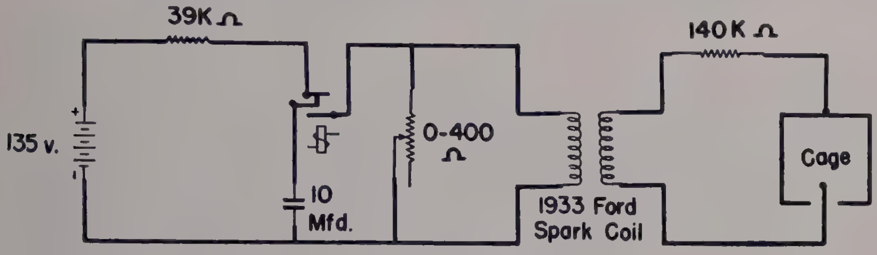


FIGURE 1. Monkey shown in Apparatus II.

Shock 1, to humans, feels like a very slight tingle. Shock 6, which is very painful, will jump an air gap of just under ½″.

Preoperative Procedures. Initial training: All animals were first trained on the highest shock intensity, No. 6. Three of the animals had previously had experience with panel-pushing for food reward, and transferred quite readily to the new situation. Each of the other four animals was trained by first delivering a train of shocks until the animal merely approached the lever, then later touched the lever, and finally pressed the lever. This process took from four days to three weeks, with approximately half an hour of testing daily.



SHOCK CIRCUIT

Figure 2

"Avoidance threshold" training: Details of the testing schedule will not be described here, since they will be submitted in a future manuscript analyzing the effects of the lesions on the avoidance thresholds. After initial training, all animals, sooner or later, were tested on each of several shock intensities, starting from the weakest in the series. Each animal was run, 40 minutes per session, on a given shock value for several days, until his daily rate became stable. Stability was defined by establishing a criterion in which the number of presses *and* the number of shocks received could not vary by more than a certain amount in a five-day period. In the case of the weak shocks, an additional criterion was established which was satisfied if an animal received at least 200 shocks within a 30-minute period on 2 successive days. The avoidance threshold was arbitrarily defined as the lowest intensity of shock which was sufficient to elicit behavior which would keep the number of shocks in a 30-minute period *under* 200, or more than an average shock rate of 6.667/min. (If an animal did not respond at all, he received 24 shocks/min.)

A typical record obtained for one of the animals on shock No. 5 is shown in FIGURE 3. This record cumulated all the responses the animal made, each response having moved the pen vertically by a small increment. The paper was moved horizontally at a constant rate. The pen automatically reset to "0" whenever a complete vertical excursion was made. This curve indicates how many responses an animal made in a given period of time, and the slope of the curve is a direct measure of the animal's over-all rate. Each little pip on the line indicates a shock.

In FIGURE 4 is shown the response records of this same animal on the ascending series of shock intensities. Note the increase in rate of response, and concomitant decrease in number of shocks delivered as the shock intensity grew stronger.

Drug experiments: After completion of avoidance threshold training (which occupied a matter of some weeks), the animals were tested under the influence of reserpine (Serpasil), pentobarbital sodium (Nembutal), and, in addition, some animals were tested after administration of isotonic saline. Shock No. 5 was used for all animals except one (S-194) which was tested on No. 6, since his threshold was 5. These values were sufficient, in all cases, to produce a high rate of response, which kept the number of shocks down to a low number.

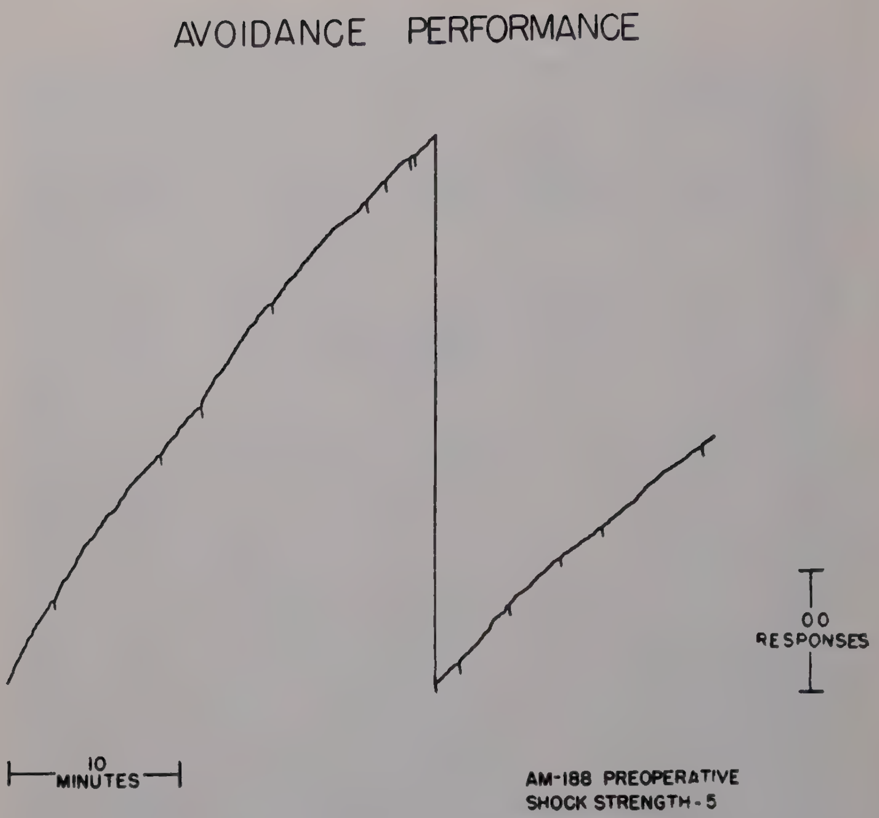


FIGURE 3. Typical cumulative performance record. See text for explanation.

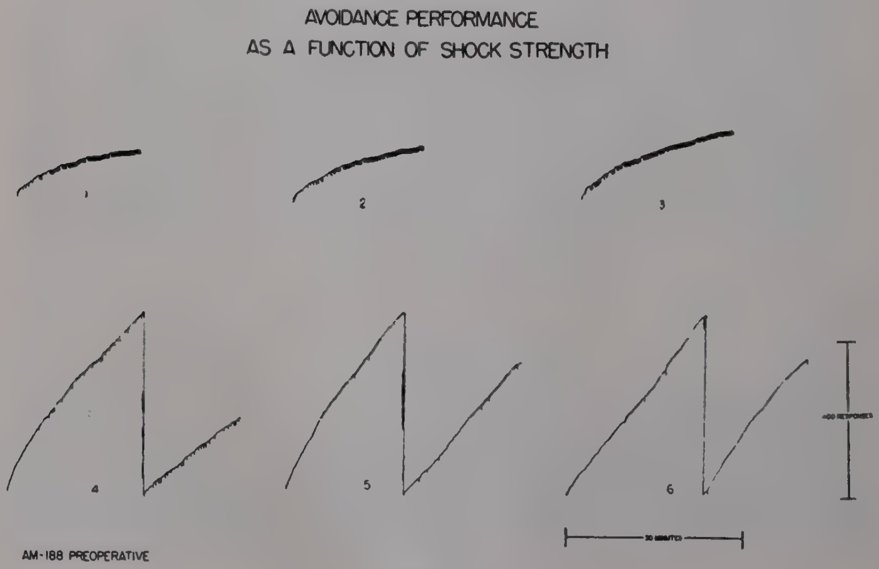


FIGURE 4

These experiments were conducted in the following sequence:

(1) First a normal control level was re-established by running the animals for two sessions.

(2) All animals were then tested following an intramuscular injection of reserpine (.75 mg./kg.). Each animal was tested when the drug seemed to have made it more docile and pettable, but before a deep state of sedation had been reached. This was accomplished within 150 to 245 minutes.

(3) A few days later, well after the gross effects of reserpine had worn off, Group I animals were run again in a normal session.

(4) All animals were next tested under pentobarbital, using an intramuscular injection of half the calculated anesthetic dose (18 mg./kg.). The criterion for desired depth of effect was that the animal should be staggering, but just well enough coordinated to grab a peanut held above his head. This was achieved within 45 to 90 minutes.

(5) Next, Group I was run following an intramuscular injection of isotonic saline solution, in volume the same as the pentobarbital dose (.30 cc./kg.). Animals were tested after the same interval following injection as they had been following pentobarbital.

Surgical procedure. Up to this point, to review briefly, all animals had avoidance threshold testing and testing on a high value of shock under the influence of reserpine and pentobarbital, and some animals were tested after injection of isotonic saline as well. Each animal was now given one of three brain lesions: an amygdaloidectomy (designated by AM); an inferior temporal convexity control lesion (IT); or a sham operation (S). In Group I, one animal was assigned to each of these three operate categories; in Group II, the animals were split evenly between AM and IT categories.

All lesions were bilateral and made in one stage, except for the sham lesion which was conducted in two stages. Intraperitoneal pentobarbital anesthesia was employed.

For the AM procedure, the zygoma was removed, the temporal muscle split and retracted, and temporal bone removed to expose the pole of the temporal lobe. The amygdala was visualized by gently retracting the lobe laterally. The lesion was made by means of suction, and was intended to include the entire amygdaloid complex and medial temporal pole.

In the IT procedure, the zygoma was left intact and the muscle cut slightly more posteriorly. The lesion extended dorsally to the superior temporal sulcus and ventrally into the fusiform gyrus, and was presumably limited to cortex.

The S procedure involved an exposure almost identical to the AM exposure. The orbital portion of the frontal lobes was gently retracted in an unsuccessful attempt to section the olfactory nerves.

Interrupted silk technique was used for closure of dura, muscle, and galea. Subcuticular continuous suture was used in the scalp. Animals were given a rest period of one week following surgery.

Histological analysis and reconstructions of the lesion are not yet available. FIGURE 5 shows reconstructions of lesions made in a recent study. These are ventral views of the brains—with the two at the right showing an amygdaloid region lesion, with representative cross sections, while the two at the left show

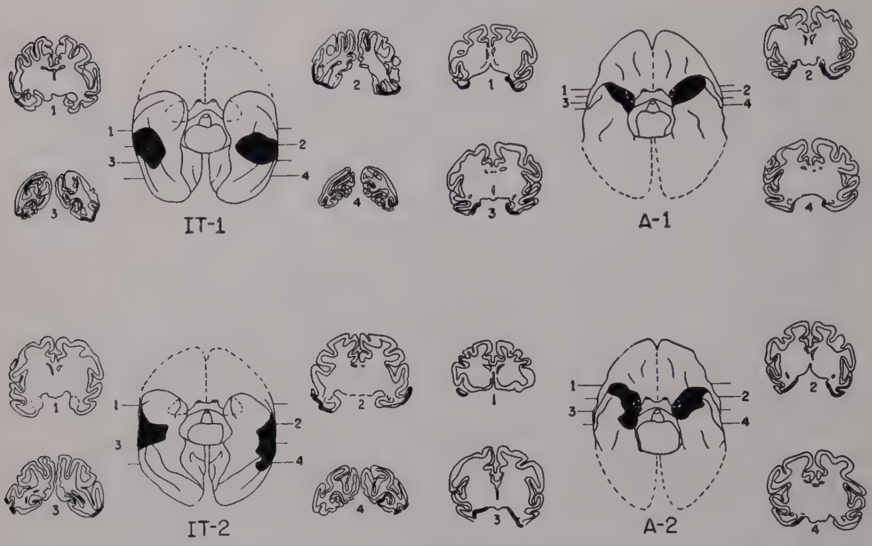


FIGURE 5. Reconstructions and representative cross sections of brains. Two figures at right illustrate amygdala region lesions (A), while two at left illustrate inferior temporal convexity lesions (IT).

inferior temporal convexity lesions. There is no reason to think that the lesions in this present study differ essentially from those illustrated in FIGURE 5, but detailed analysis of the behavioral changes due to the lesions awaits completion of the histological examination.

Postoperative training. All animals were rerun postoperatively on the avoidance threshold procedures, permitting a comparison with preoperative values. All drug procedures were repeated with the exception that no saline sessions were given.

In addition, because rather large changes were obtained in avoidance behavior following injection of reserpine, it was decided to test the animals in another situation not generally classified as "emotional." The three animals in Group I were trained in a situation where the panel-push did not delay a shock, but delivered a small pellet of food. The food was not delivered for each panel press but, rather, according to a random schedule, an animal being permitted a rewarded response once a minute on the average. Such a schedule produces a relatively stable rate of response, undisturbed by eating time or the effects of food satiation (Skinner, 1953). These animals were run for 30 minutes daily until their rates had stabilized to criterion, which all animals reached within 2 weeks. They were then run under reserpine, then again under normal conditions, and finally under pentobarbital.

Results

Effect of lesions on "avoidance thresholds." Only brief consideration will be given to the effects of brain lesions, *per se*, since, as has already been mentioned, histological examination has not yet been completed, and this paper, in any case, is primarily concerned with drug effects.

TABLE 1
AVOIDANCE "THRESHOLDS"

Animal	Preoperative	Postoperative	Difference
Group I			
AM—188	4	5	+1
IT—196	4	2	−2
S—194	5	3	−2
Group II			
AM—210	4	4	0 (+)
AM—205	3	3	0 (−)
IT—208	1	1	0 (−)
IT—207	4	1	−3

Summary for Groups I and II

	Increase	Decrease
AM	2	1
Control	0	4

The two cerebral lesions appeared to have had somewhat opposite effects. On the average, animals with amygdalectomies required a slightly more intense shock postoperatively in order to elicit avoidance behavior, while the inferior temporal controls (as well as the sham operate control) required considerably less intense shock. These results are listed in TABLE 1, together with a summary of the number in each group who increased or decreased their thresholds. When there was no difference in shock value (as indicated by "zero" in the "Difference" column), the sign indicates whether these animals received more or fewer shocks postoperatively, on the average, than they had preoperatively for that shock strength. It will be seen that two AM animals increased their thresholds, while one decreased slightly. All four controls decreased.

A more complete analysis of the behavior is given in TABLE 2. This analysis is concerned not with the threshold values, but with the animal's total performance at *all* values tested. Each entry is an average of an index comparing postoperative and preoperative performance for each shock intensity, computed according to the formula given. The responses/min. and shocks delivered/min. have been computed separately. (An average of merely the *ratio* of postoperative to preoperative performance would have been simpler, but the ratio suffers from the difficulty of approaching a limit of infinity at one extreme and tends to make, in addition, a rather biased average because of its skewed distribution. The index shown in TABLE 2 avoids such difficulties.) At the top of the table are the data for Group I; below, for Group II. A positive index means a higher postoperative rate than preoperative rate; a negative index means just the opposite. The table also summarizes the number of positive and negative indices for the two operate groups. Thus, all AM animals were slower in their responding postoperatively, while all controls were faster. Two of the three AM operates had a higher shock delivery rate postoperatively, while all controls had a lower delivery rate.

Table 2
Average Rate Indices

$$\sum\left(\frac{\text{Postop Rates}_{S_i} - \text{Preop Rates}_{S_i}}{\text{Postop Rates}_{S_i} + \text{Preop Rates}_{S_i}}\right) \bigg/ N$$

Animal	Responses	Shocks
Group I		
AM—188	−.222	+.183
IT—196	+.220	−.562
S—194	+.154	−.338
Group II		
AM—210	−.110	+.206
AM—205	−.020	−.069
IT—208	+.088	−.787
IT—207	+.504	−.990

Summary for Groups I and II

	Responses		Shocks	
	Increase	Decrease	Increase	Decrease
AM	0	3	2	1
Control	4	0	0	4

One important fact should be stressed. While it required a higher shock to elicit avoidance behavior in the AM operates, on the average, the avoidance performance of these animals at very strong intensities was very rapid and adequate. In no sense was the habit "lost" following operation. These ani-

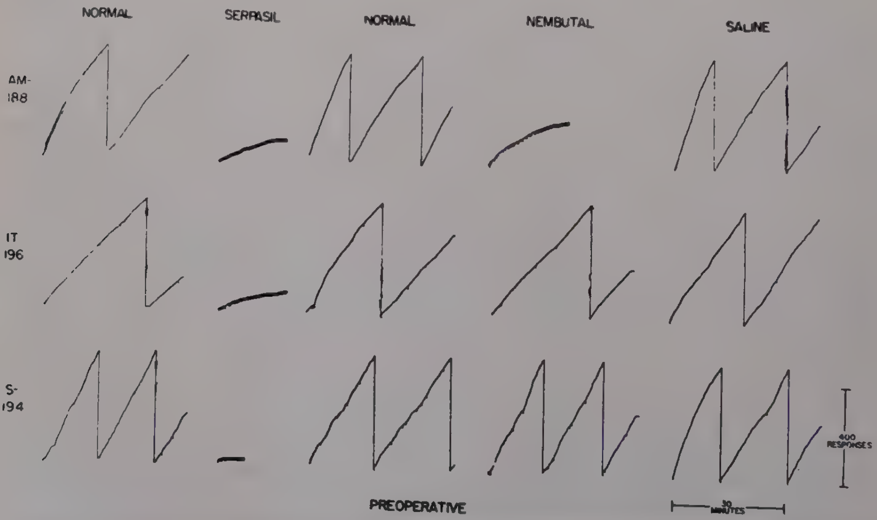


Figure 6. Preoperative performance records of Group I under normal conditions and under influence of drugs.

mals merely required stronger "electrical prodding," relative to controls, to demonstrate sustained avoidance behavior.

Effects of drugs on avoidance behavior. Preoperatively: The effect of the lesions on avoidance behavior, while definite, is dwarfed when compared with the effect of reserpine. FIGURE 6 shows the preoperative performance records for Group I. Note the low rates of response under reserpine. Pentobarbital had a rather pronounced effect in one animal, but still not as severe as the reserpine. Saline, it is interesting to note, had a slightly enhancing effect on rate.

FIGURE 7 shows the performance records for Group II. Essentially the same effects were obtained.

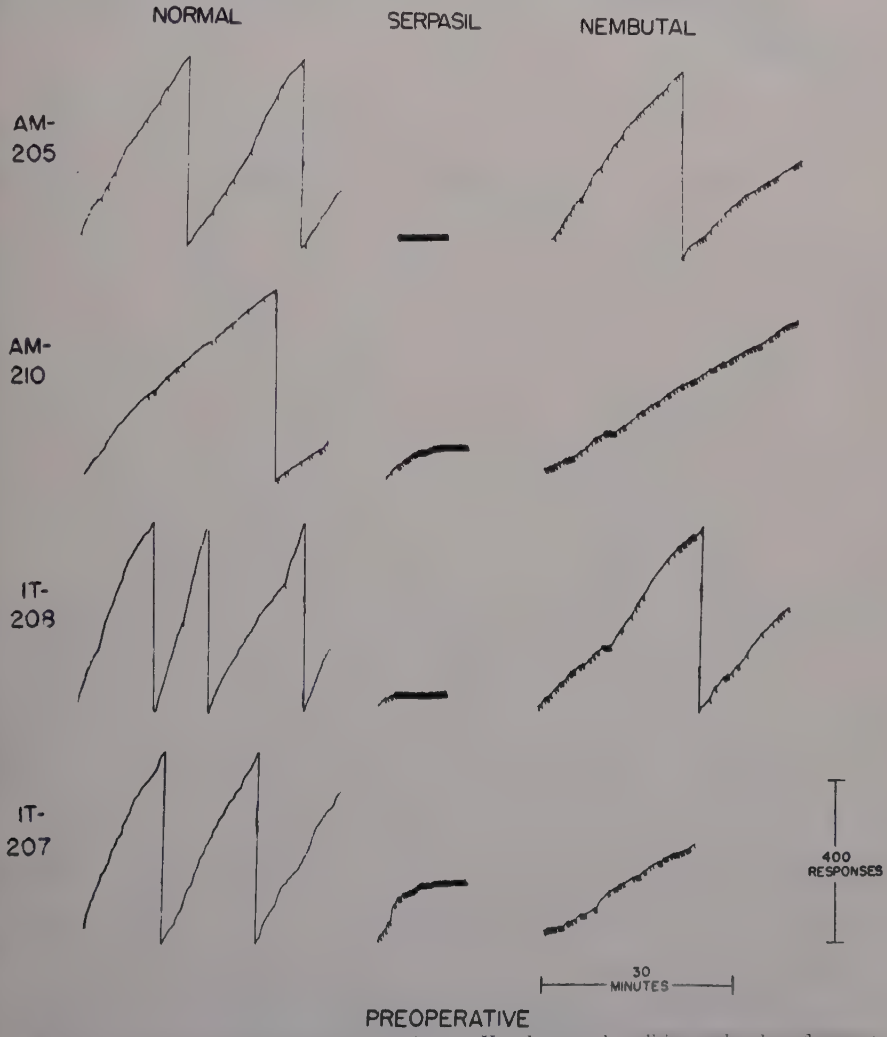


FIGURE 7. Preoperative performance records of Group II under normal conditions and under influence of drugs.

In a number of cases, a rather special kind of behavior under reserpine was noted. FIGURE 8 shows an enlarged view of one of the records. Note the even spacing between shocks. What this animal was doing was pushing the lever immediately after the shock had been delivered, thereby delaying the next

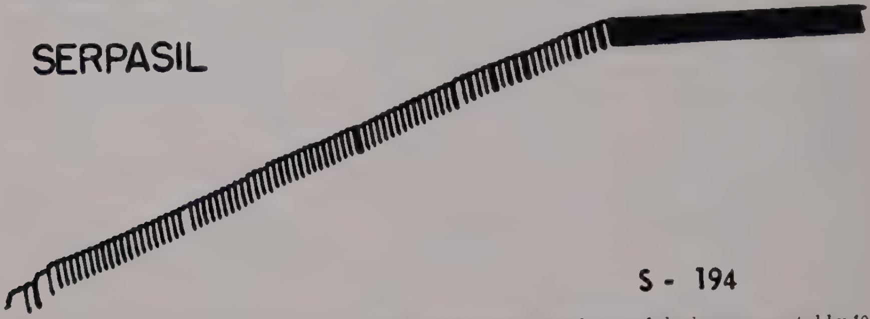


FIGURE 8. Performance record of animal S-194 under reserpine. Evenly spaced shocks are separated by 10 seconds.

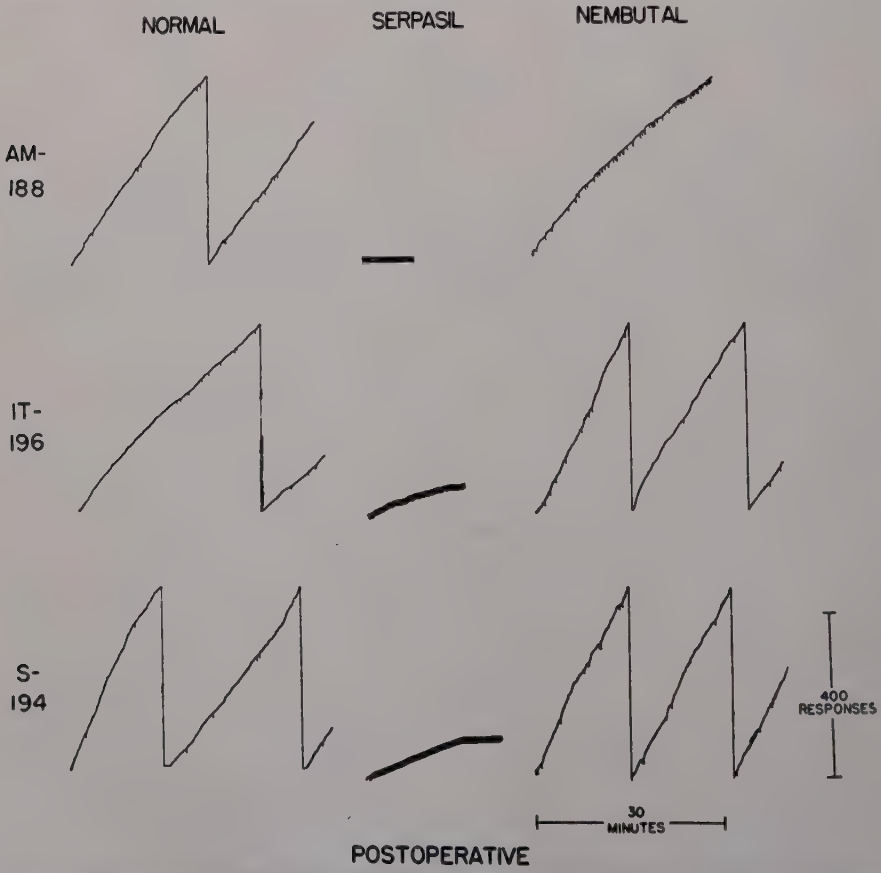


FIGURE 9. Postoperative performance records of Group I under normal conditions and under influence of drugs.

shock by 10 seconds. But, he only rarely pressed in between or in "anticipation of" shocks. Hence, he regularly received a shock almost every 10 seconds. This change in behavior can be characterized as the loss of avoidance or anticipatory responses, while escape responses remain intact. Later, as occurred *inevitably* under reserpine, this animal stopped responding completely.

Such a sustained regularity of shock intervals under pentobarbital was never observed. In many cases, the records indicate a decrease in rate of response. If one were able, however, to count all of the attempted responses made by the animals under pentobarbital, the total would probably indicate an increase rather than a decrease in rate for all animals, since many of the animals' swipes at the bar were clean misses or insufficient in force to depress it.

The reserpinized animals presented a markedly contrasting picture. In all

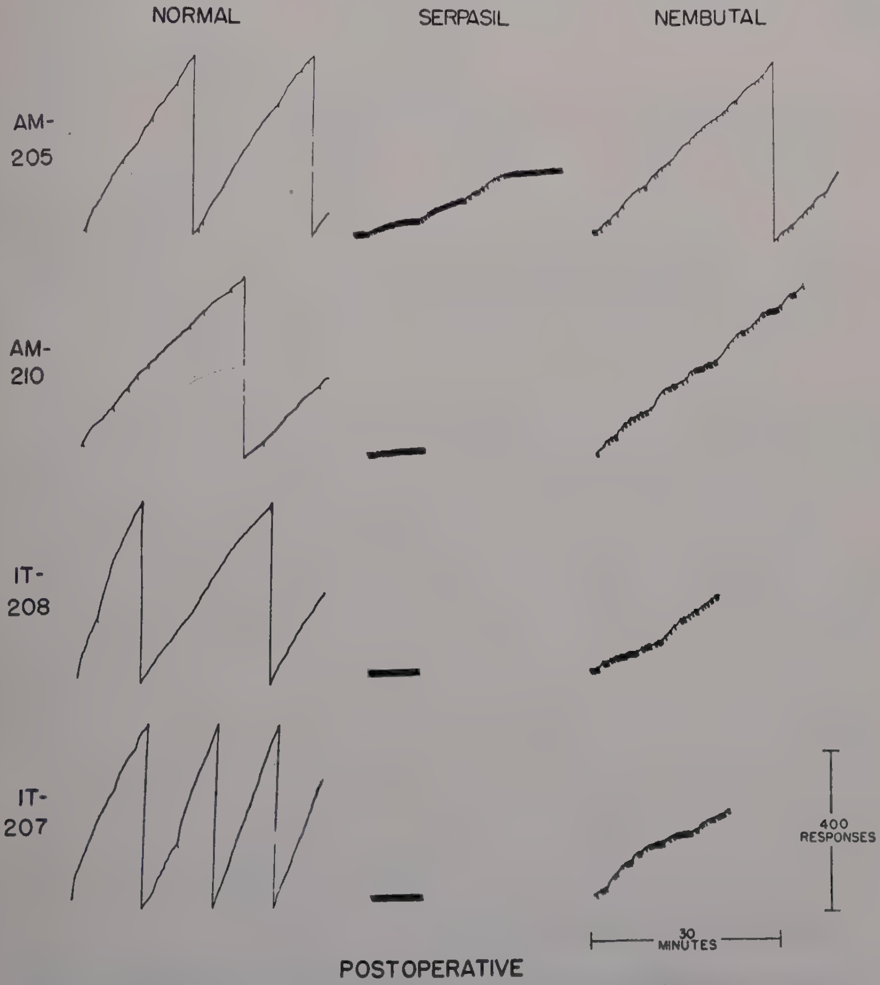


Figure 10. Postoperative performance records of Group II under normal conditions and under influence of drugs.

instances, they jumped vigorously whenever a shock was delivered, but then seemed quite unconcerned. Between shocks, they sat quietly in a hunched over position. While there may have been an analgesic effect, there was no question that they responded to the shocks.

Postoperative: The effects of both reserpine and pentobarbital were roughly the same postoperatively as preoperatively. FIGURES 9 and 10 show the performance for Groups I and II postoperatively. In FIGURES 11 and 12, pre-

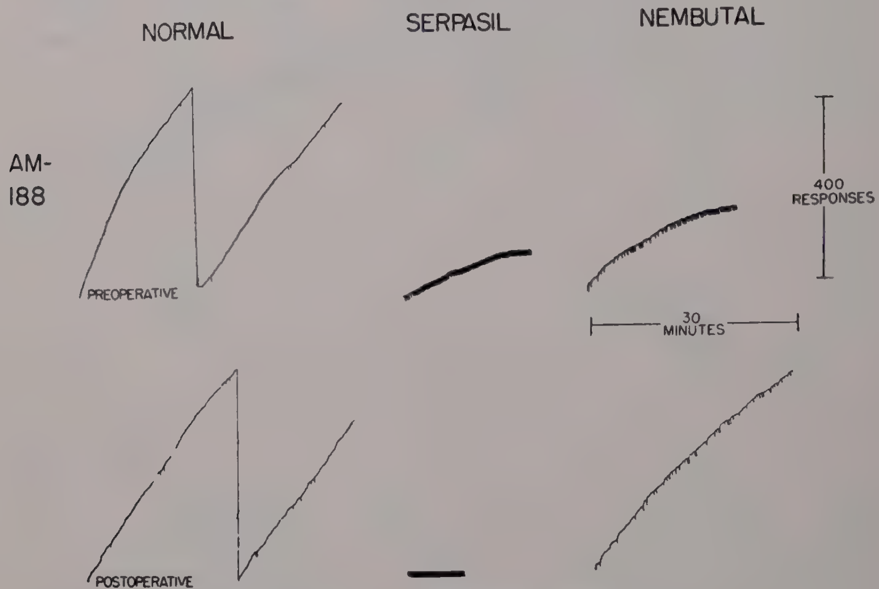


FIGURE 11. Comparison of preoperative and postoperative performance records for animal AM-188.

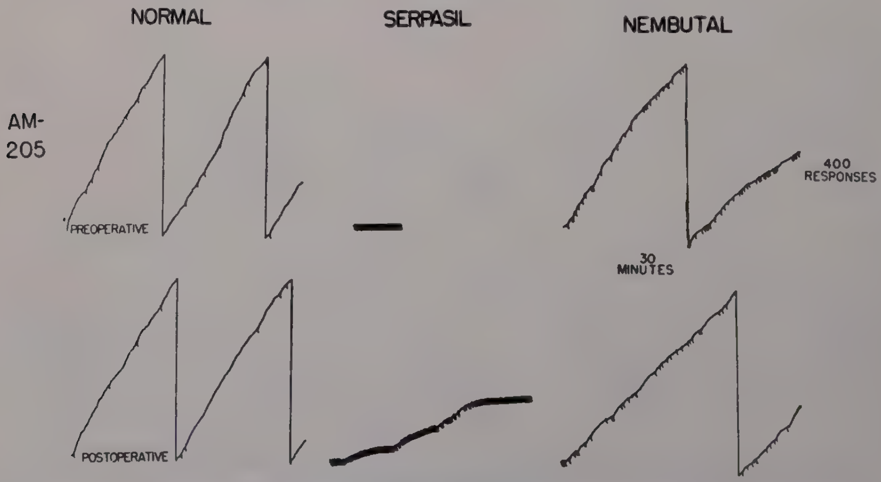


FIGURE 12. Comparison of preoperative and postoperative performance records for animal AM-205.

TABLE 3
GROUP I
RATIO OF RATES UNDER VARIOUS CONDITIONS TO NORMAL RATES

Animal	(Normal Rates)		Reserpine / Normal		Normal / Normal		Pentobarbital sodium / Normal		Saline / Normal	
	Preop	Postop	Preop	Postop	Preop	Post-op	Preop	Postop	Preop	Post-op
					Responses					
AM—188....	19.700	19.280	.238	0	1.328	—	.334	.749	1.220	—
IT—196.....	15.067	20.867	.328	.265	1.199	—	1.396	1.257	1.493	—
S—194......	24.700	23.121	.139	.196	.955	—	1.231	1.272	1.063	—
Average...	19.822	21.089	.235	.154	1.161	—	.987	1.093	1.259	—
					Shocks					
AM—188....	.150	.313	81.407	77.450	.447	—	83.333	8.201	.330	—
IT—196.....	.167	.193	86.299	69.083	.796	—	.599	1.036	.171	—
S—194......	.216	.173	99.208	65.659	2.005	—	1.236	3.468	.191	—
Average...	.178	.226	88.971	70.731	1.083	—	28.389	4.325	.231	—

operative performance is compared with postoperative performance for two individual animals. There is no evidence that an amygdaloidectomy made any difference to the effectiveness of reserpine. The occurrence of the evenly-spaced "escape" responses under reserpine was also frequently noted postoperatively.

It is not really proper, of course, to compare directly the preoperative and postoperative performance rates under a drug, since the operation itself had some effect on the control level of rate. In TABLE 3, therefore, we have compared for Group I animals, the drug rates with normal control rates both preoperatively and postoperatively. The first column shows the preoperative and postoperative normal rates, while successive columns show the ratio of rates under various conditions to these normal preoperative and postoperative rates. The upper table shows the data for responses made per minute, while the lower shows the shocks received per minute.

Note, as we have already seen, that reserpine was effective *both* preoperatively and postoperatively in producing marked reductions in response rate with concomitant increases in shock rate. Note also that, while the average ratio in *response* rate under pentobarbital is close to one, the shock rate is much higher than one, reflecting perhaps the effect of incoordination. Also note the slight increase in response rate under saline.

TABLE 4 shows comparable data for Group II animals. The table at the bottom is a summary for all seven animals. It shows the number of animals in each group in which reserpine had either an increased or decreased effect postoperatively as compared to preoperative ratio values. There is no consistent direction of change. From this summary table we conclude that reserpine is just as effective in an operated as an unoperated animal.

TABLE 4
GROUP II DATA
RATIO OF RATES UNDER VARIOUS CONDITIONS TO NORMAL RATES

Animal	(Normal rates)		Reserpine / Normal		Pentobarbital sodium / Normal	
	Preop	Postop	Preop	Postop	Preop	Postop
			Responses			
Group II						
AM—205	25.960	22.184	.031	.194	.555	.700
AM—210	13.250	14.463	.435	.080	.719	.816
IT—207	29.267	42.480	.373	0	.296	.155
IT—208	34.667	25.200	.099	0	.460	.440
Average	25.786	26.082	.234	.068	.508	.528
			Shocks			
Group II						
AM—205	.234	.283	103.598	49.678	9.401	4.947
AM—210	.867	.350	17.745	60.151	7.074	16.908
IT—207	.017	.017	855.588	1426.000	393.588	632.352
IT—208	.133	.033	143.218	734.606	27.120	225.909
Average	.313	.171	280.037	567.608	109.296	220.029

Summary for both Group I (see TABLE 3) and Group II (above)

	Responses		Shocks	
	Increase	Decrease	Increase	Decrease
AM	1	2	1	2
Control	1	3	2	2

Food reward results. The results of the food reward experiment with Group I animals, conducted after the other experiments were completed, are shown in FIGURE 13. Reserpine depressed the food responses almost entirely. No animal, at the end of the session, would pick up and ingest food when the experimenter delivered it to the food dish, but if it were actually held in front of his mouth, he might chew the food for a while. Notice the only slight effect of pentobarbital. It should be mentioned that previous investigation has shown that amygdala operates are not altered in their rates of response to this same schedule of food reward (Weiskrantz, 1953).

Discussion

Little question remains that, under the conditions of this study, reserpine has a severely depressing effect on avoidance behavior of the rhesus monkey. We have not attempted to study the effects of different doses or different time intervals on behavior; obviously, a whole set of parametric relationships re-

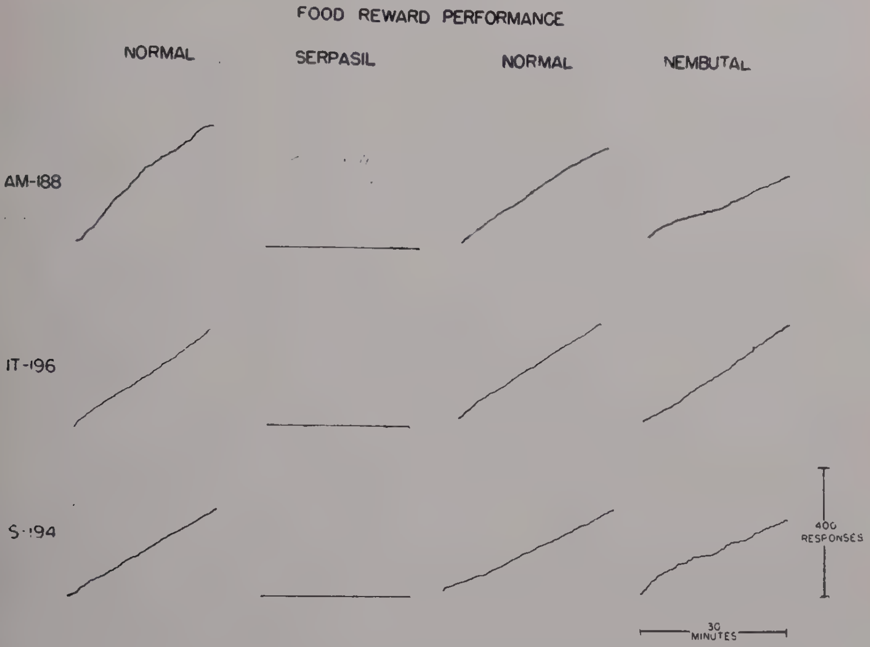


FIGURE 13

mains to be explored. It should be repeated, however, that the animals were tested at a time when the gross effects of the drug had not approached their maximum degree, and it seems highly probable that even what little behavior was observed in this project would have been completely depressed had a longer time interval been permitted to elapse between injection and behavioral testing.

The evidence, however, that food rewarded responses are also depressed would seem to indicate that the drug has a rather general effect on behavior, although it is likely that a hierarchy of behaviors could be established with further investigation, employing, for example, the type of multiple schedule recently developed by Ferster (Ferster, 1954). The fact that, in a number of cases, the rather special type of reserpine response record was obtained in which animals responded only *after* a shock had occurred, but did not avoid subsequent shocks, suggests that behavior occurs only when there is strong external stimulation to maintain it. Even well-established patterns of behavior seem incapable of maintaining themselves without such external control—*e.g.*, an animal might chew a few times on a bit of food, but then "forget" that it is in its mouth. A new piece of food might start off a few more chews. In view of the observed lack of anticipatory responses, an interesting question arises. Assuming that animals will fail to respond to conditioning procedures while under the influence of reserpine, will they also fail to exhibit the *memory* of them once the sedating effects have worn off; *i.e.*, does reserpine merely depress *performance*, or does it also depress *learning* capacity? Investigation is now in progress regarding this question.

Although many similarities in behavior exist between a reserpinized animal and an amygdala operate, the effect of the present investigation has been to point out some essential differences. For one thing, the amygdala operate is still capable of well-maintained avoidance behavior, albeit higher intensities of shock are required relative to controls.* It is perfectly possible that, with higher shock intensities, reserpinized animals would also exhibit avoidance behavior. Nevertheless, within the limits tested here the operation has less of an effect than the drug. Second, the depressing effects of amygdala lesions have to date been demonstrated only for "emotional" behavior. In other situations, such as responding for food on a random reward schedule, discriminating visual patterns for food reward, or delayed response tasks, amygdala operates fall within normal limits (Pribram and Bagshaw, 1953; Weiskrantz, 1953). Reserpine, on the other hand, seems to be more general in its behavioral effects; responding for food on a random reward schedule, at least, is severely depressed. This difference was also apparent in gross observations of the two types of animals. Reserpinized animals are much more sluggish and inactive than amygdala operates, except, perhaps, for the latter's first 48 postoperative hours.

These differences, together with the finding that reserpine was just as effective in depressing avoidance behavior in an operated as in a normal animal, evidently rule out the amygdaloid region as a critical site of action of reserpine. There is another possibility closely related by experimental anatomy to that of the amygdaloid complex. It has been shown by strychnine neuronographic techniques that the amygdaloid complex (at least the cortical nucleus of the complex) is part of a larger system consisting of the prepyriform cortex, anterior insula, anterior temporal pole, and posterior orbital frontal areas, in addition to the amygdala (Pribram and MacLean, 1953). When all or almost all of this system is damaged experimentally, the effects on gross behavior are almost indistinguishable (at least, to us) from those produced by reserpine in a normal animal. At this stage, it is still impossible to state whether a mass relationship is important in assessing the results of these lesions (with the implication that an amygdaloid region lesion alone does not destroy enough of this system) or whether a *focus* exists which is actually outside the amygdaloid complex. In the latter connection, it is significant that Turner has reported that relatively small lesions which just touched the boundary of the amygdala, but remained outside its main body, produced a much greater tameness in monkeys than lesions restricted to the amygdala (Turner, 1954). Furthermore, it has been observed in our laboratory that lesions that are placed in the prepyriform cortex and anterior insula, but which just *exclude* the amygdala, produce a reserpinelike animal. Moreover, it is of great interest to note that the *acquisition* of avoidance behavior of animals with large lesions in the orbito-insula-temporal system is very much more depressed in a shuttle-box situation than is true with more restricted amygdaloid region operates (Pribram and Weiskrantz, 1955). We, together with Pribram, are currently testing such operates in the avoidance *performance* situation described in this paper.

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* Arguing against, incidentally, the claim that only the *acquisition* and not the *maintenance* of avoidance behavior is affected by amygdala lesions (Brady *et al.*, 1954).

Although an early hypothesis regarding the site of action of reserpine pointed to the hypothalamus, subsequent research has led to the notion that some of the effects are "probably due to a blockade between afferent and efferent neurones," rather than to a "direct depressant effect" on hypothalamic centers (Schneider, 1954; Bein, 1953). We do not feel that the evidence is really substantial enough to rule out direct involvement of hypothalamic centers. Even if the "blockade" notion is accepted, it is almost meaningless to make the assumption of a "purely efferent" hypothalamus, which seems to be an implicit assumption in the "blockade" hypothesis as enunciated thus far. "Blockade" could still have a hypothalamic locus. Furthermore, the finding that reserpine (*heavy* doses, at least) affects nonhypothalamic neural activity does not rule out the possibility of a dose-time hierarchy giving hypothalamic areas priority. Finally, while the evidence derived from hypothalamic lesions does not exclude the possibility that an extrahypothalamic control center might still be the principal site of reserpine action, the strong similarity of behavioral changes produced by lateral hypothalamic lesions in the monkey (Ranson, 1939) and by reserpine is too striking to pass unmentioned.

Nevertheless, the preliminary findings with orbito-insula-temporal lesions are of some interest with respect to the idea that reserpine might somehow prevent impulses from an extrahypothalamic modulating or activating center from reaching the hypothalamus. There is good evidence that the amygdala and orbital frontal areas of the monkey send direct fibers to the ventral medial nucleus of the hypothalamus (Adey and Meyer, 1952; Clark and Meyer, 1950), which has been implicated in emotional behavior (Wheatley, 1944) and metabolic activity (Hetherington and Ranson, 1942) of cats and rats. Stimulation of the cat's amygdala yields a cortical "arousal" or "activation" pattern (Feindel and Gloor, 1954), which suggests that it might have an "activation" role somewhat analogous to that proposed for the reticular formation.

Analysis of the possible site of reserpine action has mainly followed the following pattern: As an independent variable, reserpine is administered, and certain consequences are either noted or measured as dependent variables, *e.g.*, "relaxation," "sedation," blood pressure changes, miosis, *etc.*; or else the effect of reserpine is noted on some other independent-dependent variable relationship, *e.g.*, carotid sinus reflex, decorticate sham rage, avoidance behavior, *etc.* Once these are established, a given part of the nervous system is isolated (brainstem section) or "activated" (hypothalamic stimulation) or destroyed (ciliary ganglion destruction; amygdala lesion) and changes in the consequences or in the relationships noted.

Of all the dependent variables employed for these studies, the behavioral ones are among the most difficult and complex. Yet they are certainly among the most important. The widespread use of reserpine in clinical psychiatry is based almost entirely on its behavioral effects. In a more general sense, our understanding of the mechanism of action will not be achieved *without* reference to the behavior of the affected organism. No matter how many physiological steps are filled in concerning the action of reserpine, the causal chain will not have been completed until the behavioral consequences have been determined.

This is tantamount to saying that the behavioral consequences *must* be studied sooner or later and, fortunately, can be studied independently of and prior to the investigation of physiological mechanisms. Indeed, the present state of our knowledge indicates that the analysis of behavior is very likely to *suggest* physiological foci of action, given knowledge of the effects of lesions and electrical stimulation of the central nervous system on behavior. The hypothalamic hypothesis was based largely on the similarity of the reserpine behavior to behavior produced by hypothalamic lesions and stimulation. Our present hypothesis concerning the possible role of the orbito-insula-temporal areas is based on similar evidence. Given the importance of behavioral research, it should follow that the same scientific rigors that apply to other disciplines must apply here. Gross observations are important, but they can scarcely be given the status of more than preliminary observations which may guide subsequent analytic research.

Summary

Seven rhesus monkeys were tested in an avoidance performance situation under normal conditions and following injection of reserpine (Serpasil) and pentobarbital sodium (Nembutal). Animals were then retested following a bilateral amygdaloidectomy, a bilateral control lesion in the inferior temporal convexity, or a control sham operation. In addition, three of the animals were tested postoperatively in a food reward situation under normal conditions and under drug conditions. The following results were obtained:

(1) Amygdaloidectomized animals required a stronger electric shock relative to control operates to display avoidance behavior under normal conditions.

(2) Both in the preoperative and postoperative animal, reserpine depressed avoidance behavior very severely, while pentobarbital depressed it only slightly or not at all.

(3) Reserpine, in some cases, produced a unique pattern of responding in which shocks were "escaped" but not "avoided."

(4) Food rewarded responses were almost entirely depressed by reserpine, while pentobarbital only slightly depressed such responses.

Similarities and differences between the effects of lesions and drugs are discussed as well as hypotheses regarding the possible site of action of reserpine.

Acknowledgments

The authors wish to thank Doctor Karl H. Pribram for his performance of some of the surgery in the project, and for his services as a constructive critic. Miss Lila Rupp was of invaluable assistance in constructing the figures and graphs. Robert Cox assisted with the design of the shock circuit. Reserpine (Serpasil) was kindly supplied free of charge by Ciba Pharmaceutical Products, Inc., Summit, N. J.

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A COMPARISON OF CORTICAL AND SUBCORTICAL BRAIN WAVES IN NORMAL, BARBITURATE, RESERPINE, AND CHLORPROMAZINE SLEEP*

By Russell R. Monroe, Robert G. Heath, Walter A. Mickle, and William Miller
Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, La.

For several years, the authors have been recording cortical and subcortical activity from chronically implanted electrodes in animals and humans in various states of altered awareness.[1] These states included naturally occurring phenomena such as sleep, pathological behavior such as schizophrenia and other illnesses, and pharmacologically-induced states of altered awareness.[2, 3] The dramatic tranquilizing effects of reserpine and chlorpromazine that have been noted both in published reports and in our own experience immediately led us to investigate the possible electroencephalographic changes which might accompany the use of these drugs.[4] Clinical observations have indicated that the most dramatic effect of these drugs was the reduction of spontaneous motor activity. Thus they offered a method of controlling maniacal aspects of behavior whether associated with affective or schizophrenic psychosis. In clinical use, we found, as others have reported, that, with rare exception, the psychiatric ideation remained the same.[4] Our clinical results have been inconsistent and unpredictable when these drugs were given in an attempt to control chronic tension in psychotic and neurotic patients. One striking observation, however, was that these drugs, unlike the usual barbiturate sedatives, did not produce central depression. The patients were easily aroused, and were at no time ataxic or confused. The subjective complaint of "dopiness" or being "drugged" was absent. Some of our more introspective patients who could report their feelings would describe sensations of weakness, lassitude, or a feeling of paralysis. One patient said, "I was quiet but didn't sleep."

Scalp EEG's seemed to support this subjective evaluation. We observed the patients to be relaxed, motionless, with eyes closed and clinically asleep, but without typical sleep changes in the scalp electroencelphalographic record. The changes encountered in these recordings were those of relaxation or drowsiness. Although the patient appeared to be asleep, there was no spindling or slow-wave activity associated with deeper sleep. Additional electroencephalographic evidence of differences in pharmacological action between the barbiturates and these two drugs was the lack of the usual 20 to 30/second spindling activity characteristic of barbiturates. These findings have been reported by others.[5, 6] We have previously reported that there is often a marked disparity between the cortical and subcortical recordings, as well as equally marked electroencephalographic differences in the various subcortical regions.[1, 2a, 3] The present study was inaugurated in an effort to clarify problems concerning the site of action of these drugs and to compare their effects with those of barbiturate sedatives.

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* Aided by a grant from the Commonwealth Foundation, New York, N. Y.
Reserpine (Serpasil) provided by Ciba Pharmaceutical Products, Inc., Summit, N. J. Chlorpromazine (Thorazine) provided by Smith, Kline and French Laboratories, Philadelphia, Pa.

Material and Methods

This study is the report of 46 electroencephalographic studies made on eight patients who were to receive subcortical electrical stimulation for therapeutic reasons. Six of these patients were chronic schizophrenics who had been ill for many years and had not responded to the conventional somatic therapies or psychotherapies. One patient was an adolescent with acute rheumatoid arthritis; the other, a patient with terminal cancer. The therapeutic rationale for treating these patients has been explained elsewhere.[2a] Electrodes were implanted in the septal region in all patients, and also in at least one of the following additional areas: hippocampus, amygdaloid nucleus, caudate nucleus, hypothalamus, and tegmentum of the mesencephalon. Electrodes were located on the pia arachnoid in the frontal, parietal, occipital, and temporal cortical regions. Deep electrodes were implanted by stereotaxic means implemented by ventriculography.[2c] In addition, six monkeys with similarly implanted electrodes were studied. FIGURE 1 is an illustrative example of the electrode implantation on patient A-19 showing the electrodes in place.

The subjects of this study received 2.5 to 10 mg. of reserpine intravenously after a baseline cortical and subcortical recording had been obtained. Some of the patients had been on oral medication of reserpine for several weeks prior to the intravenous dose. When chlorpromazine was tested, the patients were given a slow intravenous injection of 50 to 100 mg. diluted in 20 cc. of saline. While being studied, the patient rested quietly on an ordinary hospital bed in a dimly lit sound-attenuated room. He was observed through a one-way mirror and communication with him was maintained through a two-way speaker system. Comparative studies were made on the same subjects in normal sleep and in sleep following 0.5 gm. of intravenous Sodium Amytal. Combinations of Amytal and reserpine were also studied but as yet no studies have been made on the combination of Amytal and chlorpromazine. Brain waves were recorded on an 8-channel Grass machine for as long as 24 hours after the drug was given. In several patients, recordings of 5-minute duration were made every 15 minutes throughout the night.

Normal Sleep

To establish a background for comparison, we shall first describe the subcortical and cortical recording of normal sleep.

Gibbs[7] has reported that sleep in adults between the second and fourth decade (all but one of our patients fell in this age group) is accompanied by a characteristic chronology of changes in the scalp EEG. He states that, as drowsiness approaches, the record flattens and slows slightly. As very light sleep approaches, parietal humps are seen, frequently accompanied by positive spikes which appear in the occipital leads and are repeated at 4 to 6/second. With light sleep, spindling activity of 14/second appears. As the patient goes into slightly deeper sleep, the frequency decreases to 12 or even 10/second. Moderately deep sleep is characterized by irregular slow waves at ½ to 3/second intermixed with 4 to 8/second activity, and very deep sleep shows 1½ to 2/second waves with superimposition of residual waking frequencies.

Our findings in subcorticograms were in accord with this description of

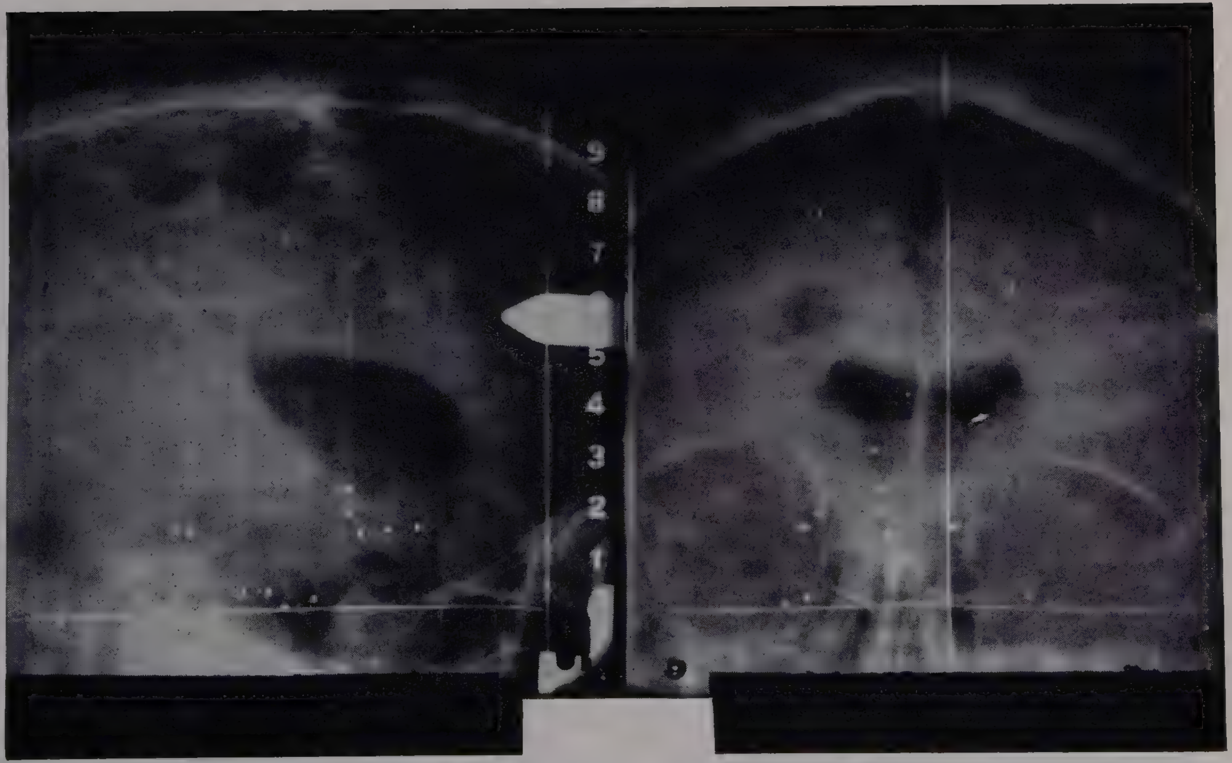

FIGURE 1. Lateral and AP X rays. Patient A-19 with electrodes in place.

Lateral view. Reading posterior to anterior (left to right), left temporal cortex, right caudal hippocampus posterior, right caudal hippocampus anterior, left hippocampus posterior, left hippocampus anterior, right hippocampus posterior, right hippocampus anterior, right caudate nucleus (superior electrode), amygdaloid nucleus (inferior electrode), right septum, left posterior septum, left anterior septum.

AP view. Right side of figure: (reading top to bottom), left frontal cortex, two left septal electrodes, two left hippocampal electrodes. *Left side of figure:* (reading top to bottom), right parietal cortex, right occipital cortex, right caudate, right amygdaloid nucleus (lateral), two right caudal hippocampal electrodes, right septum, right hippocampus anterior, right hippocampus posterior.

scalp patterns. These were most often synchronous in both the cortical and subcortical regions. Subcortical changes in the sleep pattern were most readily seen in the septal and hippocampal regions, perhaps because the amplitude from these regions was greater than in other subcortical structures. FIGURES 2 and 3 illustrate these changes with sleep. One must remember that all c

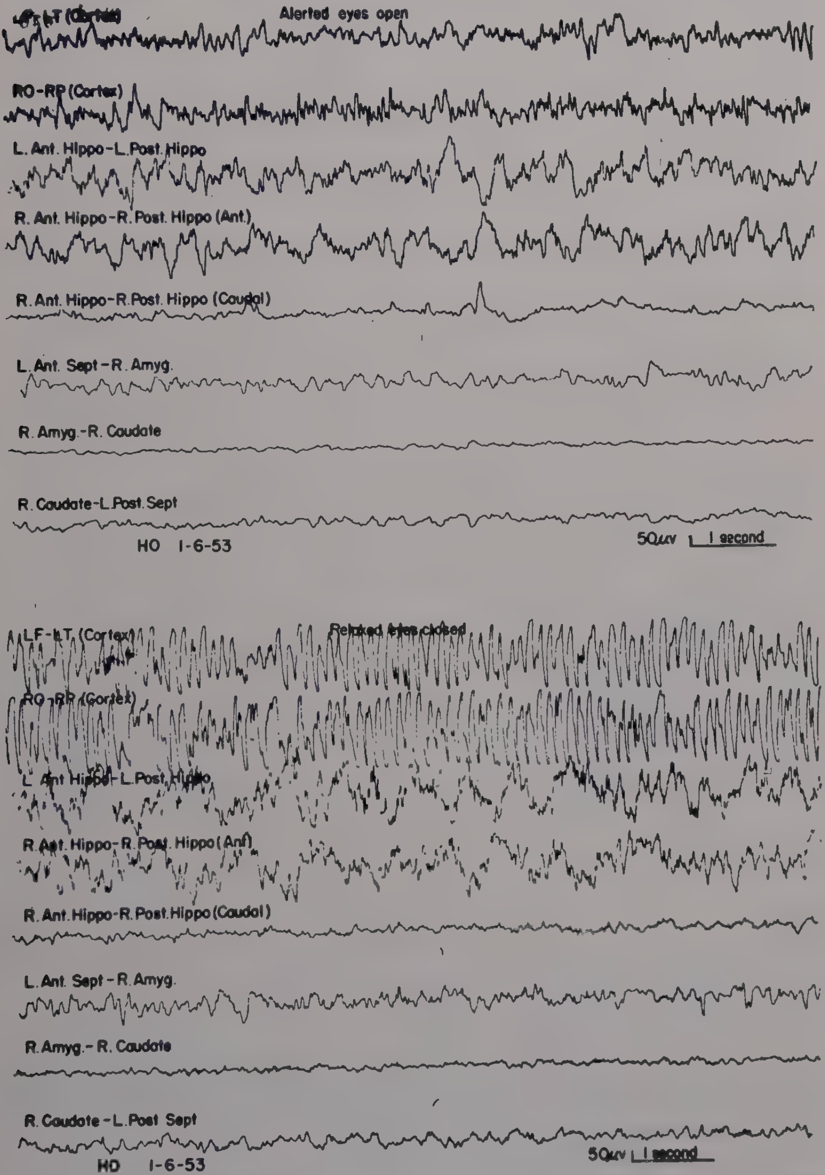

FIGURE 2. Cortical and subcortical recordings in alert state (top), and relaxed with eyes closed (bottom). Note alpha rhythm in cortical leads.

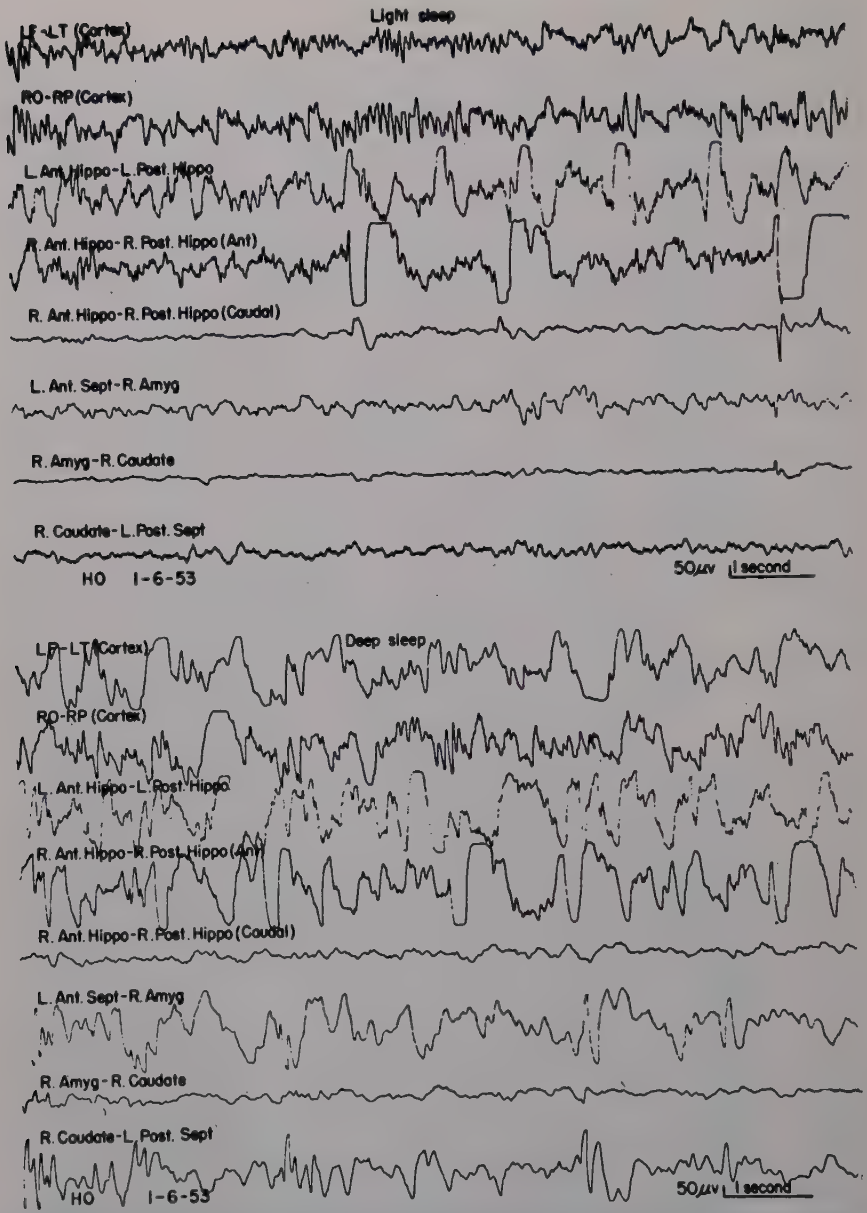

FIGURE 3. Cortical and subcortical recordings in light sleep (top) and deep sleep (bottom). Note decrease in amplitude with light sleep on the cortex and large spike and slow wave in hippocampal leads; at this stage no changes in other subcortical leads. In deep sleep note that changes are most obvious in the septal and anterior hippocampal leads.

these recordings are from electrodes directly in contact with the brain tissue or arachnoid. It has been our experience that the amplitude of activity from our arachnoid electrodes is about three times that of the scalp records. On some occasions, EEG patterns similar to deep sleep were recorded from the subcortical electrodes without homologous activity in the cortex. FIGURES 4 and 5

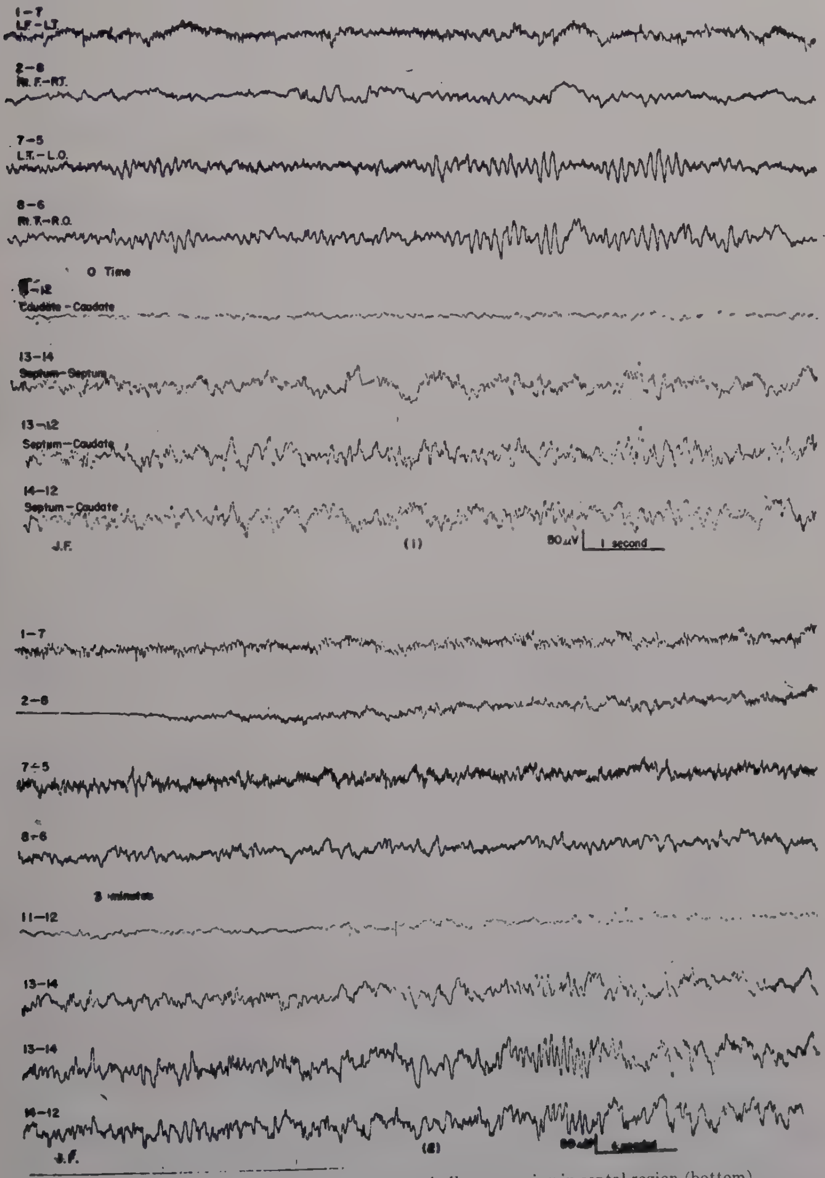

FIGURE 4. Alert record (top), and sleep spindles appearing in septal region (bottom).

are examples of this. We originally thought that this occasional failure of cortical and subcortical synchronization might be correlated with some of the clinical differences in sleep, particularly under drugs such as reserpine and chlorpromazine.

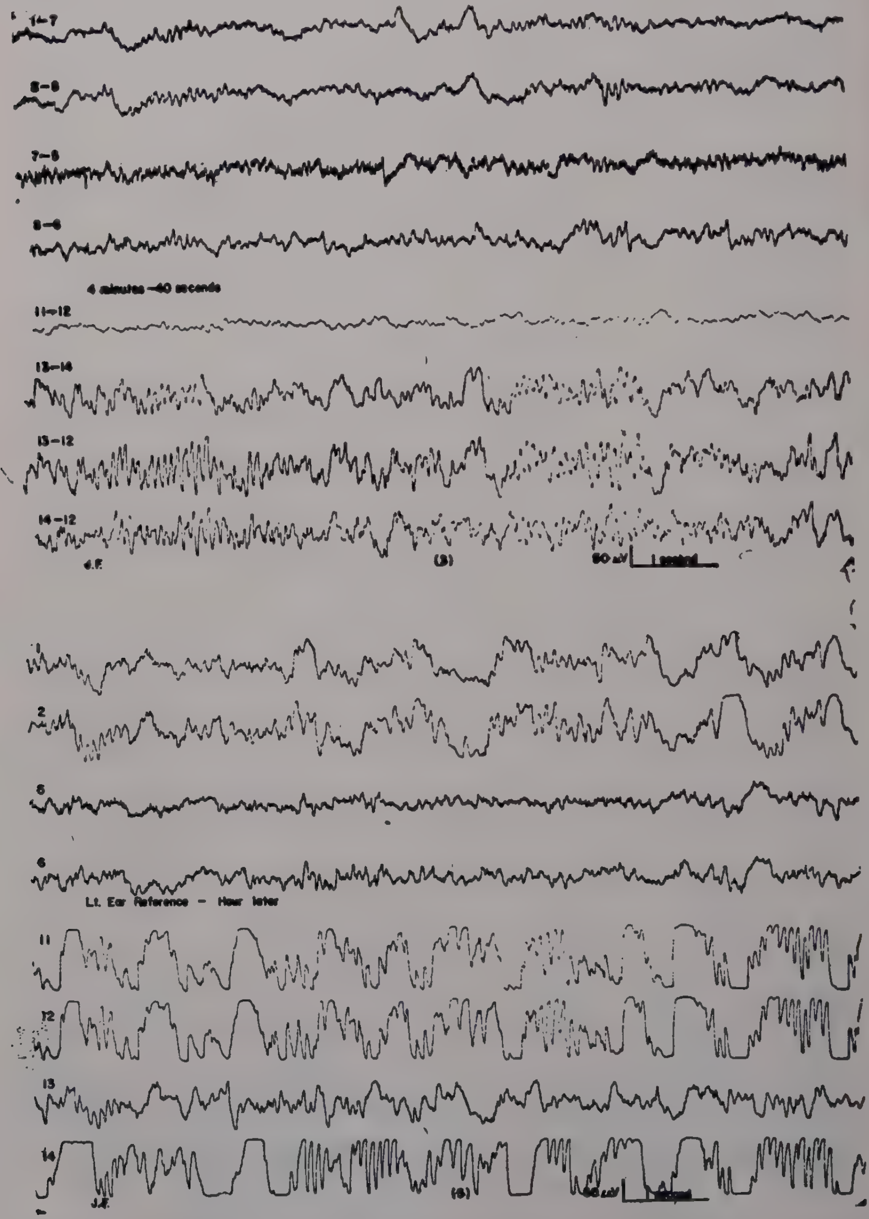

FIGURE 5. Continuation of FIGURE 4. Spindles definite in subcortex, not in scalp leads (top). Cortex now shows characteristic sleep record (bottom).

We made one additional observation, the significance of which is not clear at the moment. This is illustrated in FIGURE 6. Here we see an extremely high amplitude (often greater than 500 microvolts) spike and slow wave, which occurs most frequently in the hippocampus but is often synchronous in both hippocampal and septal regions. Since only schizophrenics had hippocampal electrodes implanted, we are not certain whether this is characteristic of all individuals as they go into sleep, or whether it is related to the specific disease process in schizophrenia. This spike has both similarities to and definite differences from the septal spike reported elsewhere that is thought to be characteristic of schizophrenia.[2d]

Reserpine and Chlorpromazine

Having received 5 to 10 mg. reserpine intravenously, the patients would generally relax within 15 minutes, or even earlier if they had not been too disturbed. After this, they remained motionless for long periods, closed their eyes and, on observation through the one-way mirror, appeared to be asleep. If they were approached quietly, however, they would usually open their eyes, smile, or express some recognition. Sometimes, they would report feeling sleepy, but often not. In fact, they would usually deny having been asleep. The sensorium was clear immediately upon opening their eyes. Occasionally, they appeared to be in somewhat deeper state of sleep and responded only if their names were called. They breathed deeply and slowly, with a sound much like a snore. Cortical and subcortical electroencephalograms taken during the periods of apparent sleep showed only a relaxed or a drowsy record. Occasionally, a momentary run of very light sleep occurred for periods of no longer than ten seconds. A comparison of relaxed records without drugs and those taken

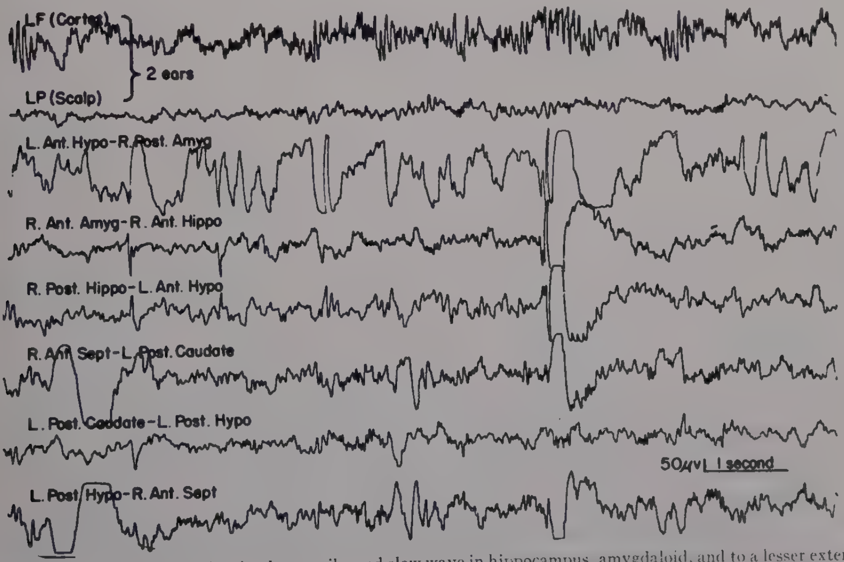

FIGURE 6. Light sleep showing large spike and slow wave in hippocampus, amygdaloid, and to a lesser extent in the septal region.

under reserpine revealed no differences between the two (FIGURE 7). These findings were consistent, whether the patient had received a single intravenous dose from 5 to 10 mg. reserpine, or had been on an oral dose of 3 mg. reserpine per day for periods of one week to one month after an initial dose of 10 mg. intramuscularly.

There was no spindling activity in the 20 to 30/second range as seen under barbiturate sedation. In one patient (FIGURE 7), however, bursts of low amplitude 30/second waves appeared in the caudate nucleus and frontal cortex. This appeared when the patient was not on reserpine and has been noted occasionally in scalp recordings on adolescents during sleep (Gibbs[7]).

The possible effect of depressant drugs on the mesencephalic reticular activating system suggested the investigation of changes in this area with these drugs. Reserpine was tested in two monkeys with chronically implanted electrodes in the medial tegmentum. As will be seen in FIGURE 8, the changes which occurred under the drug included the appearance of cortical and subcortical slow waves that are typical of a drowsy pattern in the monkey. This was also apparent in the tegmental leads, but to no greater degree than elsewhere.

It seemed obvious in one patient, and suggestive in the others, that reserpine might even prevent deep sleep. For instance, patient A-19, a simple schizophrenic with rather impoverished emotional responsiveness and little in the way of psychotic ideation, invariably went into deep sleep during routine electroencephalographic recordings. After administration of reserpine, he appeared asleep and, in fact, seemed to be snoring, but at no time did he show evidence of deep sleep in the recordings. Other patients occasionally went into deep sleep, but this was less frequent than without medication. In an effort to test the possibility that reserpine might prevent deep sleep, several patients were subjected to all-night recordings. This was carried out first without medication, then repeated after they had been on reserpine 3 mg. daily for one week, with 10 mg. intramuscularly one hour before the recording started. Five-minute recordings were made on two patients at 15-minute intervals from 10:00 o'clock in the evening until 7:00 the next morning. The first patient so tested showed the same amount of deep sleep while receiving no medications as he did on reserpine. The second patient, on reserpine, went to sleep 15 minutes earlier than he did when receiving no medication. Otherwise, the records were identical until 4:00 o'clock in the morning. Subsequently, the patient showed slightly more deep sleep while on reserpine than he did without medication. The significance of this finding is doubtful, however, because, unbeknown to the observers, the night the patient had no medication, he wet the bed, and hence was probably more uncomfortable than the comparable period when he was on reserpine. Although more patients will have to be studied to clarify this point, we think we can definitely say that there is no dramatic difference between the amount of deep sleep one sees when the patient is on reserpine and when the patient is receiving no medications at all.

Studies on four monkeys and four humans receiving 50 to 100 mg. of chlorpromazine intravenously gave similar results, namely a relaxed record with

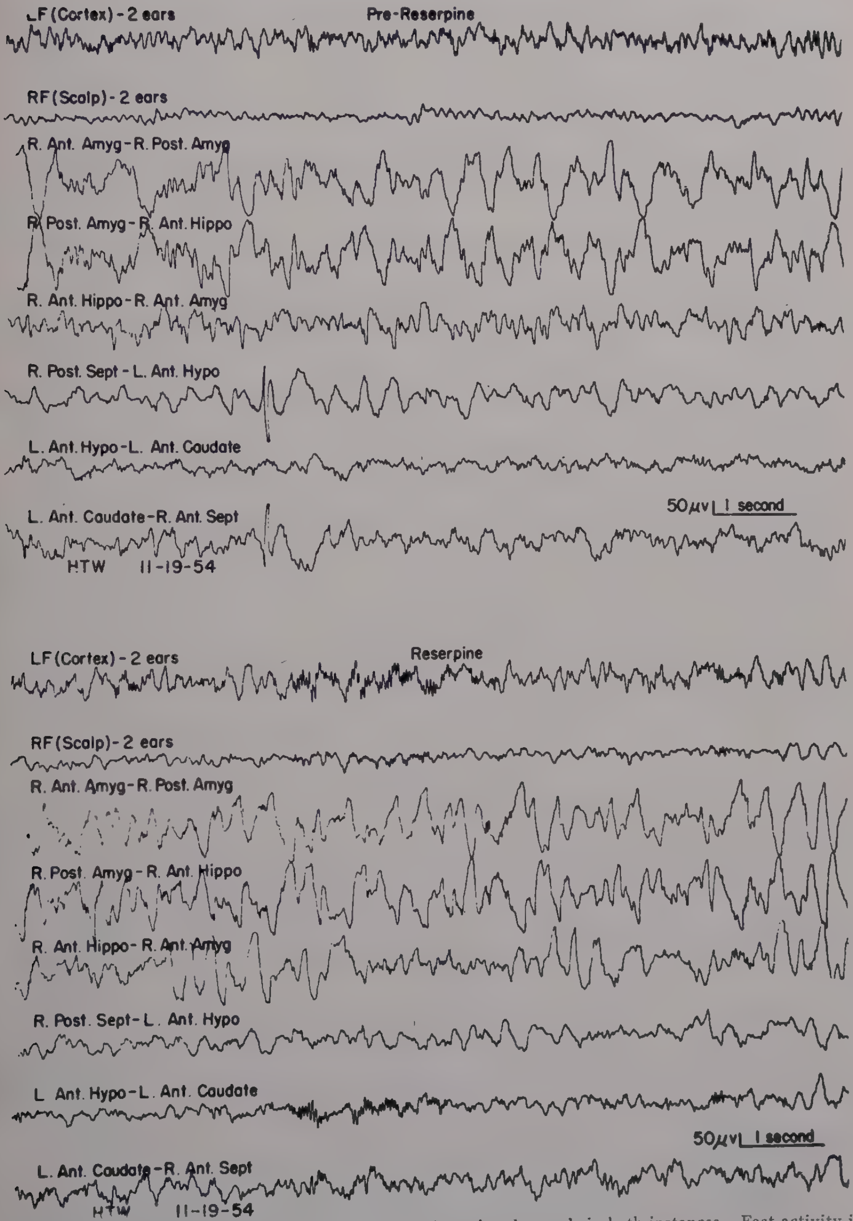
LF (Cortex) - 2 ears
Pre-Reserpine
RF (Scalp) - 2 ears
R. Ant. Amyg - R. Post. Amyg
R. Post. Amyg - R. Ant. Hippo
R. Ant. Hippo - R. Ant. Amyg
R. Post. Sept - L. Ant. Hypo
L. Ant. Hypo - L. Ant. Caudate
50μv 1 second
L. Ant. Caudate - R. Ant. Sept
HTW 11-19-54
LF (Cortex) - 2 ears
Reserpine
RF (Scalp) - 2 ears
R. Ant. Amyg - R. Post. Amyg
R. Post. Amyg - R. Ant. Hippo
R. Ant. Hippo - R. Ant. Amyg
R. Post. Sept - L. Ant. Hypo
L Ant. Hypo - L. Ant. Caudate
50μv 1 second
L. Ant. Caudate - R. Ant. Sept
HTW 11-19-54

FIGURE 7. Prereserpine and reserpine records showing relaxed records in both instances. Fast activity in caudate and frontal cortex was also noted in the baseline recording (see text). Spike in septum prereserpine record also seen after reserpine. This spike found in schizophrenics.[2d]

short bursts of drowsiness and occasional light sleep, during which time the subject was motionless, with eyes closed, appearing asleep, but easily aroused (FIGURE 9).

Other changes in behavior of the patients in the laboratory were obvious

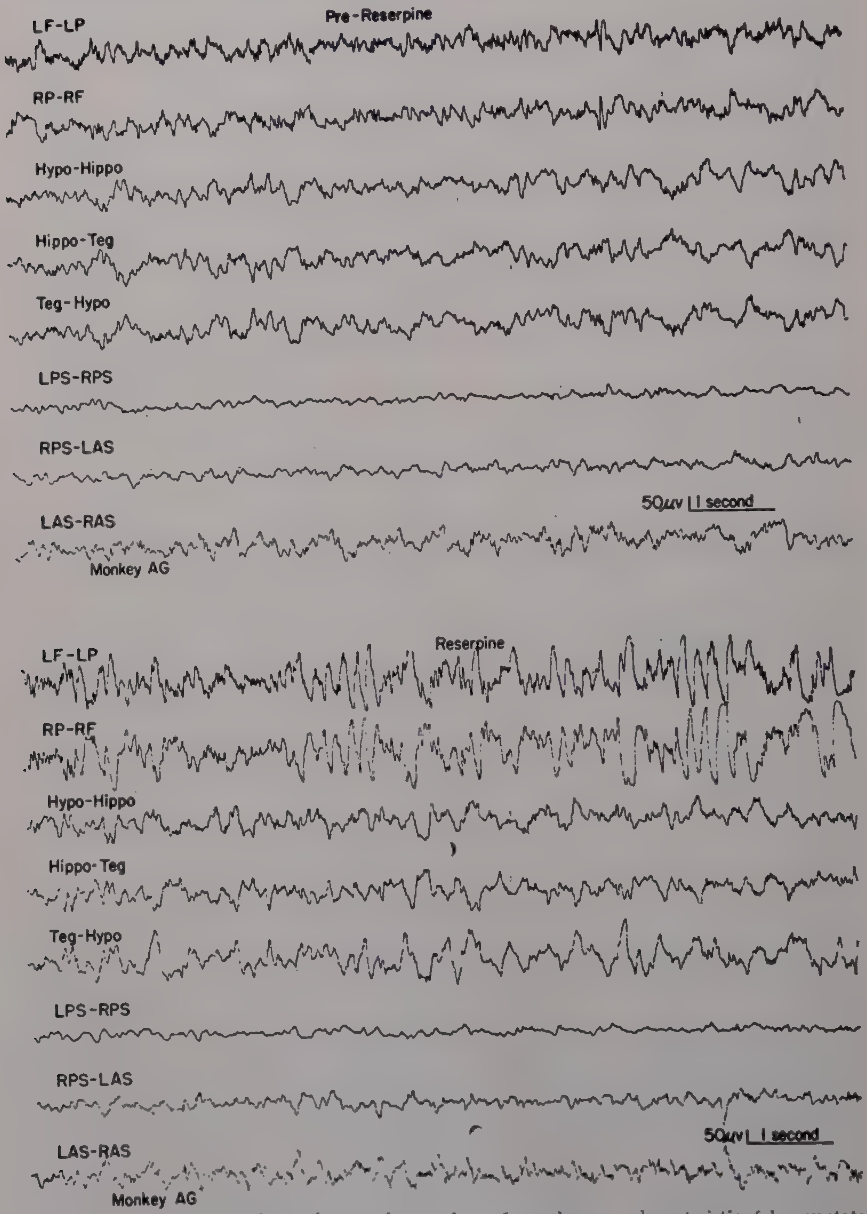

FIGURE 8. Prereserpine and reserpine record on monkey. Large slow wave characteristic of drowsy state in monkeys. Leads 6, 7, and 8 are all in the septum. Note also slow wave in tegmentum.

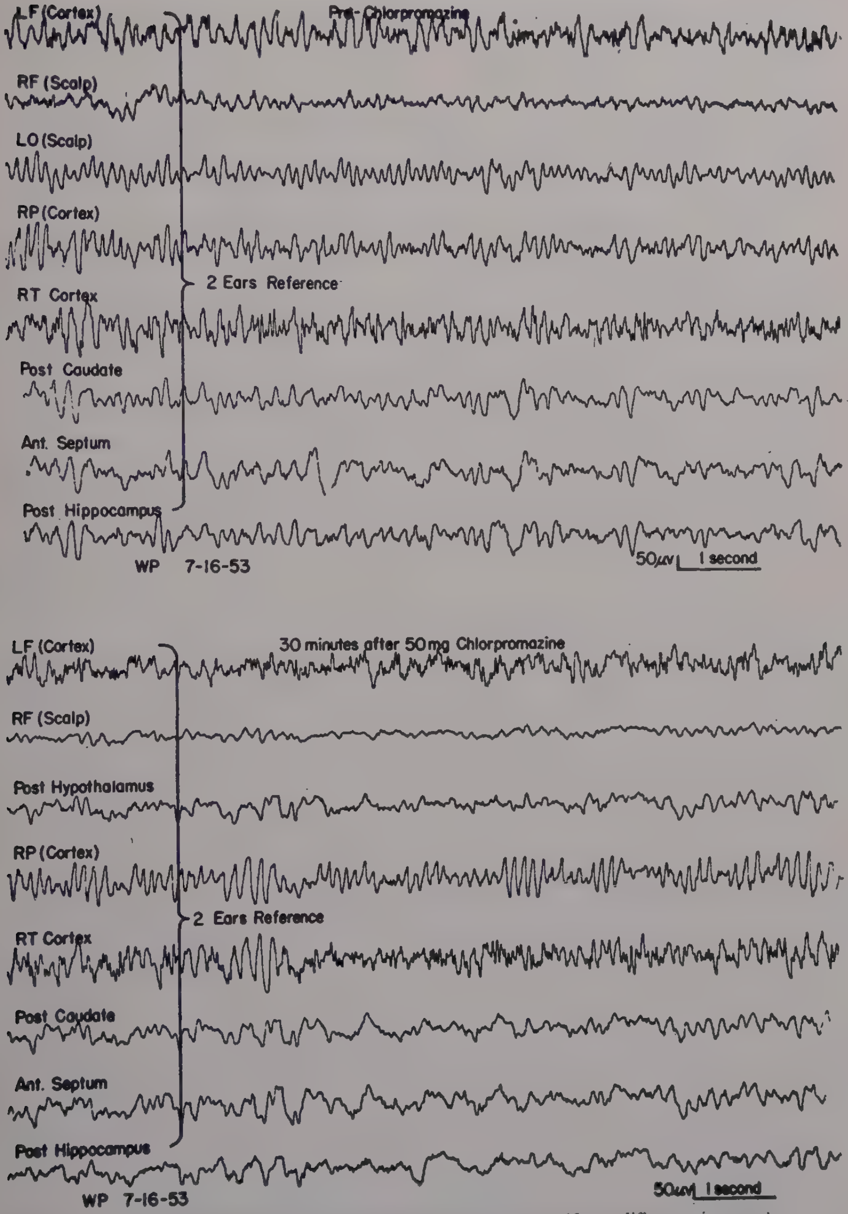

FIGURE 9. Prechlorpromazine and chlorpromazine records. No significant difference in records.

after administration of reserpine and chlorpromazine, especially if the patient were overactive or uncooperative. The patient immediately became relaxed and followed instructions. If the negativism took the form of mutism or passiveness, however, the medication produced no change in the patient's behavior

For instance, unlike the effect of Amytal, there was no facilitation of reporting conscious or unconscious material.

At the height of the drug effect, the monkeys also appeared to be asleep. Like the patients, however, they were readily aroused. When aroused, they were passive and tame. They could be taken out of restraints and easily handled, whereas previously they were normally aggressive and fearful.

Combination of Sodium Amytal and Reserpine

Our clinical evaluations were inconclusive with regard to potentiation of the barbiturates by chlorpromazine and reserpine. We have not as yet tested the combination of chlorpromazine and Amytal, but we have investigated reserpine and Amytal. In a previous report, we have shown that barbiturate spindling is noted in different areas of the brain, depending on whether the barbiturate is Sodium Amytal or phenobarbital. For instance, the spindling activity was predominant in the cortical region with phenobarbital, while Sodium Amytal affected both subcortical and cortical regions equally. This finding was one which suggested the value of investigating both the subcortical and cortical recordings in the two new drugs, chlorpromazine and reserpine. We thought there might be evidence for a specific pharmacologic effect in the subcortical regions which did not show up in the usual scalp recordings. This expectation did not materialize in our present study.

The technique for testing combinations of Amytal and reserpine was to give the patients a test dose of intravenous Sodium Amytal slowly, so that it might be discontinued when sleep was induced. The electroencephalographic recordings, both cortical and subcortical, were followed for a period of one hour. Several days after the Amytal response for the patient had been determined, he was given 10 mg. of reserpine intramuscularly and put on 3 mg. by mouth each day, for a period of at least one week. The Amytal injection was then repeated, as before, with the same amount administered at the same rate. The two records were then compared page by page.

There was no discernible difference in the time of onset, appearance, location, and amplitude of the barbiturate spindles when the patient was on reserpine and when he was not (FIGURE 10). This was true even if there appeared to be some clinical difference in the patient's reaction. There was a difference in the recordings which reflected the clinical observation that the patients, under combinations of reserpine and Sodium Amytal, went into deeper sleep earlier than they did while under reserpine alone or, in fact, when on either drug alone. For instance, one patient who required 1 gm. of Sodium Amytal intravenously before he appeared to be asleep and who did not show electroencephalographic evidence of deep sleep until two hours after the initial injection, readily went into deep sleep after only 0.5 gm. of Sodium Amytal when he had been receiving reserpine for a period of one week prior to the injection. Clinically, he also showed some difference in his presleep behavior. This is the simple schizophrenic who was previously described. He never elaborated on his delusions more than to say that God was talking to him and calling him bad names. He showed almost no emotional responsivity. When receiving

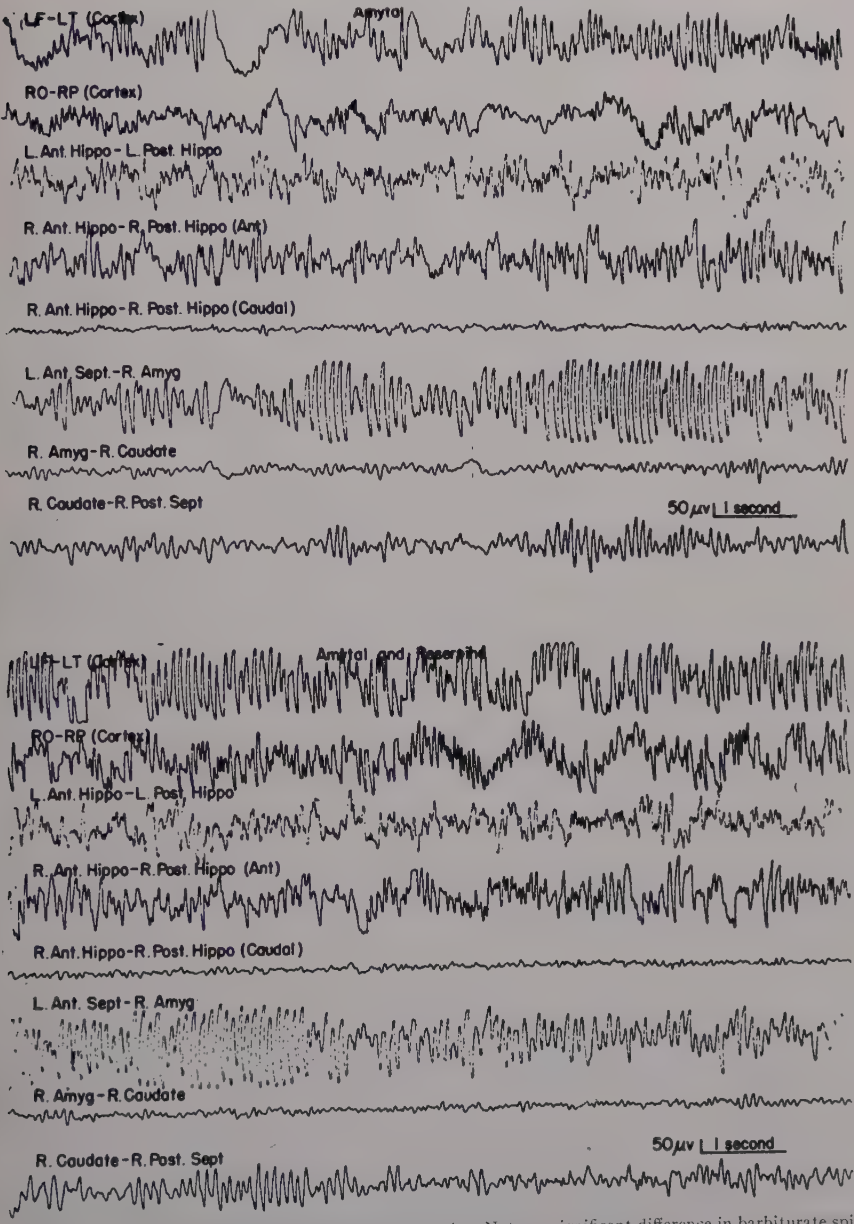

FIGURE 10. Amytal and Amytal with reserpine records. Note no significant difference in barbiturate spindling.

the Amytal injection without reserpine, he became more productive, describing in detail some of his fears of sex and women after 0.7 gm. He also described, in a somewhat embarrassed but jocular manner, the attempts of one of the doctors to hypnotize him. This was more emotion than he has shown at any other time during our observation. When on reserpine, it took only 0.3 gm. of Sodium Amytal to elicit similar behavior.

Summary

(1) Cortical and subcortical electroencephalographic recordings generally show homologous changes as the patient goes to sleep. These changes are similar to those described by Gibbs, as recorded from the usual scalp electrodes. Subcortical changes characteristic of sleep are most obvious in the septal and hippocampal regions. Rarely, one sees patterns characteristic of sleep in the subcortical structures before they are apparent on the cortex. In our patients, all of whom were schizophrenic, high-amplitude spike and slow waves were recorded from the hippocampal and, sometimes synchronously, from the septal region as the patients went into light sleep.

(2) Unlike the barbiturates, reserpine and chlorpromazine do not show any distinctive electroencephalographic changes in either the cortical or subcortical regions.

(3) Although patients with an optimal clinical effect from reserpine or chlorpromazine are lying motionless with eyes closed, their cortical and subcortical electroencephalographic records are characteristic of only resting or drowsy states. In fact, they seem to show less tendency to go to sleep than they did during baseline recordings. All night cortical and subcortical electroencephalographic recordings revealed no significant difference in the amount of deep sleep when the patients were receiving reserpine, as compared to baseline recordings without medication.

(4) Monkeys receiving chlorpromazine and reserpine showed no difference in the electroencephalographic recordings from the medial tegmentum, as compared with recording from other subcortical or cortical areas.

(5) Combinations of reserpine and Sodium Amytal induced deeper sleep than either drug alone. There was no difference, however, in the time of onset, amplitude, duration, or location of barbiturate spindling between the records of the patients receiving combinations of Amytal and reserpine, as compared with those receiving Amytal alone.

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THE USE OF RESERPINE IN AMBULATORY AND HOSPITALIZED GERIATRIC PSYCHOTICS*

By Anthony A. Sainz

Veterans Administration Hospital and State Psychopathic Hospital, Iowa City, Iowa

One of the most disturbing modern-age problems is the tenuous and ambiguous position in which older people now find themselves, faced socially with required retirement from business, unable to find work except in much less satisfactory positions than those usually available to younger persons, and more and more dependent on various welfare plans or on the charity of their offspring. In the family, the oldster is also facing less possibility of harmonious integration and becomes more of a burden, with family strife a frequent result. Physically, the aging are nowadays prone to reap a grimmer harvest not limited to the classical arteriosclerotic decay and hypohormonal, telophysiological reduction of bodily functions we so bravely group under the convenient label of "senility." To an apparently exorbitant extent, we are recipients of myriad stimuli of ecological origin that provoke diverse psychophysiological reactions. All too frequently these stimuli become chronic and are characterized by protean cardiovascular, gastrointestinal, musculoskeletal, hormonal, and other syndromes, the majority of which show prominent cerebral and psychodynamic malfunctions as principal concomitants.

All these prepsychotic and psychotic conditions become more evident and widespread with the increased longevity in the general population. The very existence of a greater number of persons in the 60-year and older-age group presents us with difficult or insoluble problems which tax the resourcefulness of physicians and place a frequently unendurable strain on family relationships. Though frequently solved by hospitalization or institutionalization of these persons, this solution brings about overcrowding of psychiatric hospitals, which are then faced with increasingly complex problems regarding intrahospital management of these patients.

Materials and Methods

A survey was made of the physical condition and psychiatric syndromology of 750 patients seen either in the Outpatient Department or hospitalized in the Mental Health Institute at Cherokee, Iowa, over a period of three years, from which it became apparent that many "senile" or "arteriosclerotic" mental dysfunctions appeared to follow complex psychophysiological disturbances and were not necessarily caused by organic cerebral changes.

Reserpine (Serpasil) was found to possess certain pharmacologic and psychodynamic actions[1] in some psychiatric conditions, and its use in the geriatric group was investigated.

In the 750 patients surveyed, psychiatric syndromology, roughly, and for practical purposes, could be divided as follows:

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* From the Research Department, Mental Health Institute, Cherokee, Iowa.

Clinical supplies of reserpine (Serpasil) courteously supplied by the Research Department, Ciba Pharmaceutical Products, Inc., Summit, N. J.

Group 1. Patients predominantly showing irritability, quarrelsomeness, apprehension, and overdependency (singly or in varying combinations). This syndrome was found in 30 per cent of hospitalized patients and in 65 per cent of ambulatory outpatients.

Group 2. Patients predominantly showing depression (with or without psychomotor slow-up), negativism, apathy, and withdrawal. This syndrome was found in 8 per cent of the hospitalized and 17 per cent of the ambulatory outpatients.

Group 3. Patients predominantly showing memory loss, confusion, disorientation, and labile emotionality. This syndrome was found in 52 per cent of the hospitalized and 18 per cent of the ambulatory outpatients.

It should be clearly understood that the above-mentioned symptoms in each case were seen singly or in combination, and that certain of them were common to all groups. Furthermore, the syndromology changed in symptom-content in about 30 per cent of the patients surveyed at unpredictable intervals. It should also be understood that all patients presented a number of somatic complaints, some clearly due to physical pathological changes, some functional, and some clearly psychogenic, either as pure psychic projections or as psychic magnifications of existing somatic illness.

The ecological and ecodynamic problems posed by these patients were summarized as follows:

Group 1. Severe problems caused by constant and repetitious demanding attitudes, dependency, latent and overt hostile behavior and disturbed moods.

Group 2. Marked problems caused by suicidal proclivities, passive uncooperativeness, refusals to eat and to perform personal necessities and great dependency.

Group 3. Mild problems, requiring only protective custodial care and some help in performing personal activities.

It was decided to use reserpine in the patients classified in Groups 1 and 2 to determine which behavior changes were affected. Results of the action of reserpine were postulated as "inadequate," if less than 50 per cent of the symptoms (or their intensity) disappeared. "Satisfactory improvement" was considered to occur when 50 per cent to 75 per cent of the syndrome disappeared, or its intensity was ameliorated by the same percentage and, at the same time, the patient was able to reach a satisfactory level of behavioral adjustment. "Remission" was considered as greater than 75 per cent disappearance of symptoms or amelioration thereof, with good behavioral adjustment.

The observed improvements had to exist continuously for at least six months to be considered valid and, in cases in which the history of the patient indicated periods of spontaneous remission, improvement had to be maintained for twice the length of the longest known period of spontaneous remission.

Eighty-nine patients were selected for this study on the basis of the prominence of their syndromology. Of these, none had had spontaneous remissions lasting more than six months. Fifty-two were females and 37 were males, ranging in age from 64 to 92 years. None of the patients, from their history or physical examination, had any overt, conclusive pathologic changes such as cerebral embolism or hemorrhage, demyelinating diseases, or infectious or toxic diseases. Diagnostically, they fell into the "senile" and "arteriosclerotic" psychotic categories, and ranged in intensity from moderate to severe. According to their symptoms, 48 patients went in Group 1, and 41 in Group 2.

Reserpine was administered orally, whenever possible, in tablet form, doses being given with meals and at bedtime. The amounts given ranged from 3 mgs. to 130 mgs. per day, and the medication was continued in all cases for a minimum of six months. Whenever oral administration was not possible, or immediate results were desired, the intravenous (i.v.) route* was used, in dosages ranging from 5 mg. to 15 mg. each from two to six times daily. Oral medication was started at 0.5 mg. with each meal and 1.5 mg. at bedtime, and was progressively increased every third day to the point at which the patients were relieved of emotional discomfort or, if this feeling did not disappear, to a point at which the patient was just short of marked lethargy. In cases where 0.25 mg./kg. of body weight (given orally) did not produce either emotional amelioration or lethargy, intravenous administration was employed, dosage being started at 25 per cent of the oral dose, and given two to six times daily. When failure to respond to initial i.v. administration occurred, the dose was increased until amelioration or lethargy appeared. All patients receiving i.v. medication were maintained under treatment for a minimum of one week, until definite emotional changes appeared, or for a maximum of four weeks.

Failure to respond to oral medication was not considered as cause for abandoning treatment, but as need to change to i.v. administration. Patients failing to respond to i.v. or combined administration in dosages up to 2 mg./kg. of body weight per day in a four-week period were considered as nonresponsive, and reserpine therefore was discontinued. Severe side effects (none of which was found) were, of course, initially postulated as mandatory indications for discontinuing treatment.

Results

Group 1. Of the 48 patients in Group 1, 40 showed remission by disappearance or marked amelioration of symptoms and, in one to six months, were reduced to small maintenance doses of reserpine in the order of 2 mg. to 10 mg. orally in divided doses, the largest of which was given at bedtime. Agitation, querulousness, irritability as expressed by labile, overreactive emotionality and, by the same token, quarrelsomeness uniformly disappeared in from 6 to 24 hours. Fearfulness and anxiety responded more slowly but were noticeably decreased in the same period. Agitation, dependency, and anxiety, however, tended to recur in most patients in about one to three weeks after start of treatment and had to be controlled with increased dosage. Gradual improvement then took place in about one to four weeks. This second improvement was lasting throughout the period of treatment (six months, including massive dosage period and maintenance dosage period), even with lowering of dosage to the maintenance level, and persisted after discontinuation of the maintenance dose. Those patients who tended to relapse after discontinuing the maintenance dose returned to good condition with resumption of the maintenance dose and did not again require massive medication. About 15 per cent of these 40 patients, for this reason, were continued indefinitely on reserpine, and have been taking daily doses from 1 to 5 mg. for about 14 months.

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* Recent work has convinced us that intramuscular (i.m.) administration is as satisfactory as i.v.

Eight severely psychotic patients in Group 1 did not show the same improvement as those described above. They had to be kept in bed under dosages above 40 mg. a day, which induced a somnolent state. They were easily aroused, however, could eat and carry out excretory functions with little help, and could locomote with some support provided by attendants. They improved noticeably, but not to an extent that they could be kept at home. They did cease to be a management problem and, at the time they were last evaluated, it seemed that they were capable of further improvement. Reserpine was continued in daily doses just below those producing somnolence and, under such conditions, the behavior and adjustment of the patients was considered satisfactory, although true psychological readaptation did not occur.

Seventeen of these Group 1 patients were first seen in the Outpatient Department, and only two of them had to be hospitalized. Our previous experience indicates that, with previously available treatment, about 60 per cent of a group of this sort would require hospitalization, and it is therefore felt that reserpine can be credited with making it possible for many more persons under treatment to continue to live at home. We feel that this is of great socio-medical importance.

Group 2. These patients responded almost uniformly with much drowsiness and depression, and psychomotor retardation either appeared or apparently increased. They became less sad and hopeless, however, more cooperative and amenable to suggestion, and those with suicidal ideas began to consider these thoughts more as an academic question than as a definite drive. Massive medication had to be given for at least one month, with only sedation and increased manageability to show for it, before hopelessness, sadness, and fearfulness began to disappear. From one to two months following the start of medication, negativism and withdrawal bowed out, and only minimal, negligible depression remained. Twenty-two of these 41 patients were considered as having undergone remission and could adjust satisfactorily. Of the remaining 19 patients in this group, 6 became manageable and cooperative but remained moderately depressed, and the rest achieved only passive manageability and retained moderate depression, negativism, and lack of motivation.

Of the Group 2 patients, nine were seen initially in the Outpatient Department. Of these nine outpatients, four improved satisfactorily and were able to remain at home on maintenance doses, one was placed in a nursing home, and four required institutionalization.

Comments and Conclusions

In the present study, Group 3 patients were not included, as it was felt their symptomatology could reasonably be ascribed to pronounced neuronal damage from toxic (alcoholism, uremia), vasculoclastic (cerebral hemorrhage, infarcts), neoplastic, infectious, traumatic, and unknown etiologies, and it is *de facto* impractical to expect any medical procedure to revive extinct cells. Since it is well known, however, that many of these cases may have more apparent than real cellular loss, a separate study of the action of reserpine in their condi-

TABLE 1

RESULTS WITH RESERPINE TREATMENT

	Number of patients	"Remissions"	"Satisfactory improvement"	"Inadequate"
Group 1	48	40	1	7
Group 2	41	22	6	13

tions was made and will be reported elsewhere. It may be said that some of them showed surprising results.

No effort was made to subject our results to complete statistical analysis other than to determine that the results obtained were from the action of reserpine and not a chance occurrence. Further validation of the experiment was made by administering placebo tablets and injections, for two weeks prior to start of the reserpine therapy, to all the 89 patients, although the ward medical and nursing personnel were told that they were actually using reserpine. No changes in patient behavior were observed during placebo treatment.

The statistical method of evaluating results was not used except for validity and reliability, because of the author's deep conviction that complex cerebral phenomena such as those presented by our material are not, in our day, sufficiently clear or homogenous to permit mathematical computation or quantification, and can lead only to misleading generalizations. Therefore, each patient was individually studied, and the reactions noted and evaluated. On the basis of such individual studies, the following conclusions were reached:

(1) Reserpine does not appear to act, in the patients studied, by altering the basic etiological factors responsible for the cerebral disturbances. It acts on cerebral areas[2] in such a way as to counteract or minimize the disturbances caused by the etiologic factors.

(2) Reserpine has a selective action on certain brain functions and appears capable of modifying these functions to a certain extent.

(3) Many of the symptoms presented by our patients are nonspecific, and may be originated by diverse causes. The beneficial effect of reserpine is due partly to symptomatic alleviation and partly to direct cerebral function modification. Therefore reserpine is not merely a palliative, but has curative action with respect to some manifestations. In other words, reserpine does not cure "mental illnesses," but does cure some symptoms thereof and alleviates others.

(4) Hyperkinetic, hyperphrenic, phrenostatic, and affective lability were the symptoms found to be either cured or remarkably improved by reserpine. Anxiety, fearfulness, and organic depression were only palliated. Thinking disturbances, memory loss, disorientation, and confusion were not directly modified, although improvements were noted in these manifestations due to modification of components involved in the underlying mechanisms.

(5) In the particular case of the "arteriosclerotic" and "senile" psychotics studied, it is concluded that reserpine shows an extremely beneficial action. It should be considered as the basic drug in the treatment of these conditions. This is not to imply that it should be used alone, to the exclusion of all other medicaments and therapies. On the contrary, it should frequently be sup-

plemented by other measures such as intensive plurivitamin therapy, analeptic drugs and, infrequently, even electrocoma therapy. In these patients, reserpine tends to decrease the emotional response to exogenous and bodily stimuli, thereby decreasing or eliminating agitation and permitting an adequate adjustment to environmental and physical stresses. Even in extreme cases, it provides emotional insulation and general sedation without interfering with apperceptive formations, thus promoting greater manageability. It also tends to minimize depression and negativism.

(6) Reserpine must be given in sufficient dosage and for a sufficient length of time. In our cases, dosages in the neighorhood of 15 mg. in 24 hours were generally therapeutically effective and maintenance doses were small (as described above), but it was only by persistently increasing dosage that success was obtained in some patients. Four patients received doses ranging from .75 mg. to 2 mg./kg. of body weight from one week to one month, without even becoming somnolent, and with eventual improvement. They are, at present, on a maintenance dose of 6 mg. to 10 mg. daily by mouth.

(7) It must be reiterated that some patients sedate and improve in the first days of treatment, only to become "worse" afterwards, either becoming hyperkinetic or depressed. This deterioration is definitely not a sign that the drug should be discontinued, but that, in excitements, dosage should be increased and, in depressions, dosage should be kept constant.

(8) Serious side reactions were not encountered. The most annoying problems were nasal stuffiness, hypersalivation, intestinal hypermotility, lethargy, and drowsiness. The Parkinsonism described by Kline,[3] and also observed by us in younger patients,[4] did not appear. It is felt that the age of our patients may play a rôle in this discrepancy.

In conclusion, it may be stated that the results produced by the use of reserpine alone in these patients were most gratifying. Many ambulatory patients were able to remain at home while under treatment, and an analysis of the behavior of the 63 hospitalized patients included in our study showed that man-hours of work spent by psychiatric aides, nurses, and doctors in their care decreased an average of 50 per cent. This reduction should be of great interest to state hospitals in general, which are surfeited, by and large, with patients in these categories.

It should be stressed emphatically that reserpine, in addition to having therapeutic properties, is a most valuable prophylactic agent for patients in the conditions described above, and may ultimately find its most definitive use as a preventive that could be used safely to reduce or eliminate the incidence of many unfortunate episodes.[*]

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[*] I cannot complete this paper without expressing my thanks to Doctor W. C. Brinegar, Superintendent of the Mental Health Institute, who suggested this project and helped throughout with his expert, valuable, and welcome advice.

PRELIMINARY OBSERVATIONS ON THE EFFECTS OF PARENTERAL RESERPINE ON CEREBRAL BLOOD FLOW, OXYGEN AND GLUCOSE METABOLISM, AND ELECTROENCEPHALOGRAMS OF PATIENTS WITH ESSENTIAL HYPERTENSION*

By J. H. Hafkenschiel, A. M. Sellers, G. A. King, and M. W. Thorner
Hypertension Section, Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, and the Department of Neurology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Reserpine has been demonstrated to be a more potent antihypertensive substance when given intravenously in adequate dosage than had been realized previously.[1] According to Moyer,[2] the hypotensive action associated with this *Rauwolfia* alkaloid is due to a generalized decrease in peripheral vascular resistance because cardiac output was not reduced. We have observed that patients experienced minimal discomfort at the time of the greatest reduction in arterial pressure.[1] The delayed reduction in arterial pressure so characteristic of reserpine might lead to a gradual release of cerebral vascular tone in the hypertensive patient, allowing cerebral blood flow and oxygen uptake to remain unchanged, so that the subject experiences no untoward symptoms that might be attributed to cerebral ischemia. To test this thesis, measurements of cerebral blood flow, oxygen and glucose uptake, and mean arterial pressure were made in five hypertensive subjects in the supine position before and after intravenous reserpine. This study is an extension of an investigation of the effect of various depressor drugs and hypotensive procedures on the blood flow and oxygen consumption of the brain in subjects with essential hypertension.[3]

Using a postural test,[4] with electroencephalograms being recorded, standing as well as supine, observations were made before, and one to eight hours after, intravenous reserpine in seven hypertensive subjects. This study was of interest because: (1) electroencephalograms of hypertensive subjects are thought by Schroeder to be abnormal;[5] and (2) tracings of a markedly quieted monkey after reserpine showed a normal pattern with very slight slowing, in contrast to the typical pattern seen with barbiturates.[6]

Methods

Hospitalized patients with moderate to severe hypertension (by Smithwick criteria, Groups II to IV)[7] were selected for these tests. They were able to lie flat for at least one hour. Most of the subjects had the electroencephalograms several days before the reserpine test. Initially, auscultatory blood pressures, pulse rates, and respiratory rates were taken. Cerebral blood flow was measured in the fasting state with the Kety-Schmidt nitrous oxide method, as previously reported,[8] the study being conducted with the subject in the supine position. In addition, blood samples were analyzed for glucose.[9] After this control observation, an injection of reserpine was given intravenously

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* This study was supported in part by Kirby McCarthy Funds and by research grants (H-361-C4 and H-1817) from the National Heart Institute, United States Public Health Service and the Ciba Pharmaceutical Products, Inc., Summit, N. J.

with a total dose varying between 2.5 and 5.5 mg. (ranging from 40 to 108 μg./kg.) depending upon how high the initial arterial pressures were. Larger doses (above 60 μg./kg.) were administered to patients with an initial mean arterial pressure above 160 mm. Hg.

Auscultatory blood pressures, pulse, and respiratory rates were recorded at five-minute intervals after reserpine, and the second cerebral blood flow measurement was begun when the pressures had remained essentially unchanged for 15 minutes, usually about 60 minutes after reserpine administration.

The patients were told that a substance had been given which would lead to a more relaxed feeling. The apparent state of nervous tension of the subject during the initial and subsequent study was estimated.[1, 8]

The patients were then returned to their rooms and their blood pressures were checked, using the postural test at three and six hour intervals after the reserpine injection. If there was evidence of a postural hypotension and, if the patient was able to complete the test of three minutes of quiet standing, one electroencephalogram was made, as soon as possible, while the patient was supine and another while he was standing. Postural tests were made at intervals subsequently, until the pretreatment blood pressure levels were reached, usually 24 hours after reserpine injection. The values of cerebral blood flow (CBF), cerebral oxygen consumption ($CMRO_2$), cerebral glucose utilization (CMR glucose), cerebral vascular resistance (CVR), and mean arterial blood pressure (MABP) were averaged to give the group result. The electroencephalograms after reserpine were reviewed by the neurologists (G. A. K. and M. W. T.) and compared with the prereserpine tracings.

Results

Table 1 contains the data on cerebral circulation and on oxygen and glucose metabolism for each patient, before and after intravenous reserpine, with an estimate of the apparent state of nervous tension. The mean values before and after reserpine for the group of five hypertensive patients are summarized in table 2. The reduction in MABP was the only significant change ($p < 0.02$) with cerebral blood flow, oxygen and glucose consumption remaining essentially constant. When compared with the changes in $CMRO_2$ after a placebo, and $CMRO_2$ and CMR glucose after carbon dioxide inhalation (our only other group with glucose measurements), there was no significant difference. After reserpine, there was no consistent change which could be correlated with the patient's apparent state of nervous tension, although all subjects were less attentive after the *Rauwolfia* alkaloid.

Table 3 contains the data on the electroencephalograms on each patient before and after intravenous reserpine. There appeared to be no obvious gross effect on the recumbent electroencephalogram that could be attributed to reserpine. Blood pressures were reduced while standing, after reserpine, about 35 per cent. Two patients (J. P. and E. R., table 3) with a marked drop in blood pressure on standing developed slow wave activity of frequency four to five per second after reserpine. The same result is well known in postural hypotension, whatever the cause. The slow wave activity, therefore, appears

TABLE 1

EFFECT OF INTRAVENOUS RESERPINE ON CEREBRAL CIRCULATION, OXYGEN AND GLUCOSE METABOLISM OF PATIENTS WITH ESSENTIAL HYPERTENSION

Patient	Sex	Age	Smithwick group	Dosage		Mean arterial pressure mm. Hg		Cerebral									
				Mgm. total	µg. per kilo			Blood flow*		Oxygen uptake*		Glucose uptake§		Vascular resistance†		Respiratory quotient	
						B‡	A**	B†	A	B	A	B	A	B	A	B	A
P. B.	F	26	IV	2.5	40	118	78	69	58	4.7	3.9	11.7	5.8	1.7[R]	1.4[R]	1.07	0.94
W. H.	M	41	IV	5.0	48	142	98	30	39	2.1	2.5	3.6	0.4	4.7[R]	2.5[R]	0.91	1.04
B. D.	M	44	IV	5.0	66	176	128	72	74	4.6	4.3	5.8	8.1	2.5[R]	1.7[R]	0.78	1.05
R. C.	F	40	II	4.5	75	160	144	45	43	3.3	3.3	3.5	4.3	3.6[T]	3.4[R]	1.22	1.07
A. M.	M	48	IV	5.5	108	173	160	34	30	2.4	2.0	3.4	1.2	5.1[T]	5.3[R]	1.08	0.76

Patient	Sex	Pulse rate per minute		Resp. rate per minute		Oxygen								Glucose, mgm. %			
						Content volumes %				Tension mm. Hg venous		Saturation % oxygen Hb venous		Arterial		Venous	
						Arterial		Venous									
		B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
P. B.	F	78	76	24	18	17.5	19.2	10.7	12.6	33	38	56	64	85	81	68	71
W. H.	M	80	68	20	24	19.9	19.0	12.9	11.0	34	30	61	53	98	100	86	99
B. D.	M	72	72	24	18	19.4	17.3	13.0	11.4	39	36	69	59	84	111	76	100
R. C.	F	72	72	18	14	14.1	13.4	6.8	5.8	28	26	53	47	84	90	76	80
A. M.	M	102	80	18	18	16.5	16.5	9.4	9.8	30	33	57	60	101	109	91	105

Patient	Sex	Carbon dioxide												Volume % packed red cells			
		Content volumes %				Tension mm. Hg				Blood pH 37°C.							
		Arterial		Venous		Arterial		Venous		Arterial		Venous		Arterial		Venous	
		B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
P. B.	F	44.6	45.0	52.0	51.2	46	47	56	58	7.32	7.32	7.29	7.26	47.4	47.0	46.9	48.2
W. H.	M	51.3	51.2	57.7	59.5	45	45	52	60	7.39	7.39	7.36	7.32	47.2	50.5	51.2	54.0
B. D.	M	49.2	48.3	54.2	54.4	44	42	52	52	7.38	7.39	7.34	7.33	45.0	45.0	45.5	46.4
R. C.	F	45.6	48.3	54.5	56.6	31	35	44	48	7.49	7.46	7.40	7.37	34.3	32.5	35.0	33.6
A. M.	M	48.6	50.0	56.2	55.2	39	42	50	50	7.43	7.42	7.38	7.35	42.0	43.0	43.2	42.8

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* Cc. per 100 gm. per minute.

† Cerebral vascular resistance is mean arterial pressure divided by cerebral blood flow expressed as mm. Hg per cc. blood per 100 gm. brain per minute.

‡ Denotes study made before drug injection.

** Denotes study made after drug injection.

[T] Indicates that the patient appeared tense during the procedure.

[R] Indicates that the patient appeared relaxed during the procedure.

TABLE 2

ESSENTIAL HYPERTENSION: CEREBRAL HEMODYNAMICS AND OXYGEN UPTAKE
Before and Sixty Minutes after Intravenous Reserpine

	Pressure		Flow		Resistance		Uptake			
							Oxygen		Glucose	
Mean of five tests.....	154	122	50	49	3.5	2.9	3.4	3.2	5.6	4.0

The figures in the left-hand column of each parameter denote the mean value before reserpine and those in the right-hand column denote the mean value approximately 60 minutes after reserpine. Pressure is mean arterial blood pressure in mm. Hg. Flow is cerebral blood flow in ml. per 100 gm. brain per minute. Resistance is cerebral vascular resistance and is mean arterial pressure divided by cerebral blood flow expressed as mm. Hg/ml. blood per minute. Oxygen uptake is cerebral oxygen consumption in ml. per 100 gm. brain per minute. Glucose uptake is cerebral glucose consumption in mgm. per 100 gm. brain per minute.

The only statistically significant change is the reduction in mean arterial pressure after reserpine ($p < 0.02$).

related to the postural hypotension effect of the drug and is not seen unless this effect develops.

Comment

These preliminary observations show that, under the conditions of these experiments, reserpine, while reducing the supine mean arterial pressure about 20 per cent, one hour after injection, does not decrease cerebral blood flow, oxygen and glucose consumption, and does not alter arterial carbon dioxide or jugular oxygen tension. A state of being less attentive gradually developed, after reserpine, in all of the subjects undergoing cerebral hemodynamic measurements. No untoward reactions other than nasal congestion were observed. Although the cerebral glucose metabolic rate was reduced about 29 per cent for this group (with a reduction of only 17 per cent observed in patients tested similarly before and after carbon dioxide inhalation[10]), the variations were not consistent enough for the observed difference to be significant. It seems likely that the decrease in CVR would become statistically significant when more patients are tested.

While it is premature to attempt to relate behavior to cerebral metabolism, especially those types of behavior known in man as intellect, we venture to provoke discussion by doing this in the attempt to understand the mechanism and locus of reserpine action.[11, 12] The question arises as to whether the quieting effect of reserpine is the result of some action on all of the cerebral cells or upon the same specific region, such as the hypothalamic area.

One conspicuous effect of reserpine other than the delayed appearance of the full effect on reducing blood pressure is the impairment of attention of individuals under the influence of this alkaloid. There appears to be no failure of memory, no impairment of either the ability to form new concepts, or to reason with previously acquired knowledge, at least in the interval of one to eight hours after parenteral reserpine. Our observations pertain only to mentally healthy subjects. No focal symptoms, such as paralysis of voluntary movement, loss of vision, tactile discrimination, and aphasia, have been noted. Thus it would seem that reserpine, in the dosage range tested, exerts its action in most subjects through a mechanism that reduces attention or produces a

TABLE 3

EFFECTS OF PARENTERAL RESERPINE ON THE ELECTROENCEPHALOGRAMS OF PATIENTS WITH ESSENTIAL HYPERTENSION

	Lying EEG	B. P.	Standing EEG	B. P.
		Before Reserpine		
J. F.	Within normal limits	180/100	No change (3 min.)	190/120
W. H.	Within normal limits	200/140	No change	195/125
J. P.	Within normal limits	255/130	No change	245/130
E. R.	Within normal limits	204/110	No change	210/120
B. D.	Within normal limits	200/140	No change	200/140
A. C.	Diffuse slow wave activity with a right temporal lobe focus (3/sec. frequency)[*]	190/120	Slow wave activity more pronounced	190/120
W. K.	Within normal limits	200/120	No change	210/130
		After Reserpine		
J. F.	Normal	150/88	Normal	160/100
W. H.	Within normal limits	120/70	No significant change	90/64
J. P.	Within normal limits	205/90	There was significant increase in 4–5/sec. slow wave activity[†]	135/90
E. R.	Within normal limits	138/80	There was some slow wave activity bilaterally 4.5–5/sec.	(1 min.) 90/? (3 min.) 118/80
B. D.	Within normal limits	130/80	No significant change	90/70
A. C.	Random slow wave activity; (3-4/sec.)	150/90	Little change in amount slow wave activity	110/80
W. K.	Within normal limits	180/100	No change	150/90

[*] This patient had symptoms referable to the left arm and, at post-mortem examination two and one-half months after this test, was demonstrated to have congenital saccular aneurysm of the right posterior cerebral artery, unruptured; thrombosis of the right posterior cerebral artery, recent; intra-aneurysmal thrombosis; recent infarct necrosis (encephalomalacia) of the right hippocampal gyrus; and compression of the right temporal lobe by aneurysm, as well as generalized cerebral arteriosclerosis.

[†] This patient had a history compatible with a cerebral vascular accident without residual neurological deficit four weeks before this test.

lesser degree of spontaneity[13] than had been apparent before the alkaloid was administered. Wilkins, in this country, first recognized the usefulness of this *Rauwolfia* effect in the management of hypertensive patients.[14]

Our findings, using the nitrous oxide technique which gives an average value per unit of brain tissue for the entire brain, suggest that reserpine does not interfere with the metabolic activities of the nerve cells in the cerebral cortex and in the cerebral nuclear masses. It is possible, but unlikely, that further work will indicate that the brain, ordinarily an obligatory glucose utilizer, is unable to extract glucose after reserpine. Gordan and his co-workers have observed no reduction in cerebral glucose uptake, after reserpine, in chronic schizophrenic patients.[15] The nitrous oxide method gives no direct information about the metabolism of specific centers of neural activity.

In recent experiments, we have not made any observations that would cause us to revise our earlier impression that reserpine *does not* lower arterial pressure simply as a function of sedation (or impaired attention or reduced spontaneity).[16] Satisfactory hypotension has not been produced in all subjects having an impairment of attention and, by contrast, hypotension has followed reserpine (with or without apparent sedation but always easy arousability) in some patients whose blood pressures had responded poorly, or not at all, to other depressor drugs or to heavy sedation with barbiturates.[17]

One of the most delicate confirmations of the fact that states of altered consciousness are expressions of neurophysiologic changes is the electroencephalogram. The electroencephalograms of the majority of the hypertensive patients included in this study were normal. In those that were abnormal, there was a clinical history of some neurological abnormality such as a hemiparesis. These data lead to the conclusion that there is no essential difference between the electroencephalograms of hypertensive and normotensive subjects. After reserpine, there is little or no alteration in recumbent electroencephalograms.[18, 19]

Thus, these preliminary investigations show that the reduced spontaneity following reserpine is not due either to a generalized metabolic disturbance of the brain or to any electrical disturbance of the cortical neurones that could be detected by the electroencephalogram. Our observations favor the hypothesis that reserpine acts upon a hypothalamic locus. The routes and mechanisms of this action are as yet unknown, but there is temporary impairment of attention, reduction of arterial blood pressure and, in some patients, lowering of the increased peripheral vascular resistance. The *long range* therapeutic value of reserpine in the management of hypertensive patients is not established by these data.

Summary

Five patients with moderately severe essential hypertension were studied in the following manner. Measurements were made of arterial and internal jugular blood gases, central blood flow, oxygen and glucose uptake, and jugular venous oxygen tension. The observations were repeated 60 minutes after intravenous administration (40 to 108 μg./kl. of reserpine, at which time the arterial pressure was reduced about 20 per cent. The high cerebral vascular resistance was reduced. Cerebral blood flow, glucose uptake, oxygen uptake, and venous oxygen tension were unchanged after this *Rauwolfia* alkaloid.

Electroencephalograms, recumbent and standing, in seven hypertensive patients were recorded before, and one to eight hours after, parenteral reserpine. After reserpine, there appears to be little or no alteration in brain waves recorded supine.

These preliminary observations suggest that the reduced spontaneity and decreased peripheral vascular resistance following reserpine in hypertensive patients is not due to a generalized metabolic disturbance of the brain. There is likewise no evidence in the electroencephalogram to suggest widespread disturbance of cortical activity.

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USE OF RESERPINE IN A NEUROPSYCHIATRIC HOSPITAL*

By Nathan S. Kline and Alfred M. Stanley
Rockland State Hospital, Orangeburg, N. Y.

There is a completely unverified story about a vacationist in the Maine woods who hired a young hunting dog named "Resident Psychiatrist" to take with him while shooting. The animal showed tremendous promise and, for a relatively inexperienced dog, was unusually good at both pointing and retrieving. The next year, when the vacationist returned, he asked for the same animal to take hunting with him. "Oh," said the man at the kennel "that animal was so good that we changed his name from 'Resident Psychiatrist' to 'Supervising Psychiatrist,' and it will cost you twice as much to hire him." This time the hound proved to be a perfect hunting dog in every imaginable respect and, when the vacationist returned the third year he naturally requested the same animal. "No," said the kennel master this time "you really don't want that dog. Toward the end of last year he got to be so good that we changed his name again and called him 'Director'. And, since that time, all he's done is sit on his fanny and yapped directions at the other dogs." This story probably illustrates the fact that the ways of directors sometimes appear strange to people in different positions. From the point of view of hospital administration, the problem is not solely whether a preparation such as reserpine will cure an individual patient, but whether the over-all therapeutic picture is improved by the addition. Does it act on large numbers of patients more rapidly, more inexpensively and more permanently than other forms of treatment for specific conditions? It is necessary to adhere to the dictum of "the greatest good for the greatest number." In addition to discharging patients from the hospital, there is the equally important problem of maintaining those patients who cannot be brought to a point of improvement sufficient for discharge in as comfortable, healthy, and economical a manner as possible. Further, although it is not the direct concern of such an administrator, there is interest in fostering whatever procedures will help keep patients out of mental institutions.

Although completely definitive answers cannot be provided as to how reserpine serves any of these functions, there is sufficient information available, as the result of our experiences over the past year and a half, to give some indication as to the likely outcome. In one form or another, we have treated well over 1500 patients, so that some of the results have statistical validity.

In our initial study,[1] results obtained on about 700 patients placed on placebo, on reserpine, and on whole root of *Rauwolfia serpentina* were compared and contrasted with results obtained under premedication conditions. The report was based on the 411 patients who could be judged under all four circumstances. Although, in the light of our present dosage regime, the 1 mg. given daily verged on the homeopathic, the results were still conclusive enough to dem-

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* Grateful acknowledgment is made to the Research Department of Ciba Pharmaceutical Products, Inc., for their provision of intramuscular reserpine in the form of Serpasil (parenteral). The Research and Development Division of the Smith, Kline & French Laboratories were kind enough to supply the chlorpromazine in the form of Thorazine. Appreciation for the supply of oral reserpine is expressed both to the Squibb Pharmaceutical Division of Matthiesen-Olin for Rau-sed, and to Ciba for Serpasil.

TABLE 1

NUMBER OF ASSAULTS

	Premedication	Placebo	Reserpine (1 mg. daily)
Females	18	15	10
Males	10	10	9
Total	28	25	19

TABLE 2

NUMBER OF RESTRAINTS AND SECLUSIONS

	Premedication	Placebo	Reserpine (1 mg. daily)
Females	326	347	284
Males	220	219	208
Total	546	566	492

TABLE 3

DAILY WARD JOURNAL DESCRIPTION

	Premedication	Placebo	Reserpine (1 mg. daily)
No. of entries	462	430	507
% Noisy	19%	19%	14%*

* Difference between reserpine and other conditions is significant at the 1 per cent level of confidence.

onstrate that the number of assaults, the number of restraints and seclusion, and the general noise and disturbance in the ward were all reduced as a result of medication. TABLES 1, 2, and 3, which are modifications of the original ones, demonstrate this result.

Instead of a standard dose of 1 mg. we are now using a minimal dose of 3 mg. orally plus the parenteral form as indicated.[2] Although we have not subjected this aspect of the problem to statistical analysis, every ward that has used the drug has uniformly reported a marked decrease in the decibel level, an increase in the cooperativeness of the patients, and decidedly less need for restraints, isolation, and seclusion. Even if the drug were found to do nothing more, it has already firmly established itself in our hospital as the method of choice for providing sedation at the present time. It has proved itself effective at times where other sedatives, pharmaceuticals, or other methods of sedation have failed and, moreover, it is free of many of the complications or side effects of alternate methods. There is relatively little danger of overdosage as compared with other medications of this type, and there is not the ataxia, dehydration, and deadening of appetite which so frequently occurs with the barbiturates. The reduction in restraints, isolation, and seclusion has allowed the ward personnel at the attendant and nursing levels to devote themselves more fully to other constructive activity than was formerly possible. Of course, there are patients whose response is only temporary so that it has not been possible to eliminate seclusion and restraint. In addition to the relief provided to individual patients who were highly excited, disturbed, and uncomfortable, the sedation of these extreme cases have made the ward more pleasant and comfortable for the less disturbed patients as well.

Our current impression is that reserpine is more than a sedative, but that it will probably require at least five years before we can decide fully whether the drug does have curative properties of a permanent nature. The results we have obtained to date are certainly worth reporting. In a report[3] that has already been accepted for publication in the *American Journal of Psychiatry*, 150 of the most disturbed psychotic females were placed on a regime of combined oral and intramuscular medication. Patients were given 3 mg. orally throughout the entire course of treatment. In addition to this medication, they were given 5 mg. intramuscularly for the first 10 days and, if the response proved favorable (not merely as sedation), the oral dose was continued, but the intramuscular dose was given on alternate days for three doses. If improvement still continued, the intramuscular medication was given every fourth day for two doses, and was then discontinued as regular medication, being used only for booster shots if such treatment proved necessary. On the other hand, if beneficial response was not obtained at the end of the first 10 days, the intramuscular dose was increased to 10 mg. every other day with 5 mg. on the alternate days. This treatment was maintained for eight days and, if there was still no favorable response, the dose was raised to 10 mg. daily for five doses. If there was still no improvement, the dose was reduced to 5 mg. daily for 3 doses, and then eliminated completely. Again, oral medication of 3 mg. was continued, so that the total treatment ran from three to four months. The patients go through three phases in treatment (as originally described by Barsa[3]). the sedative, the turbulent, and the integrative. It is important to realize that the patients often appear worse in the turbulent phase.

Of these patients, 131 had previously received insulin therapy and/or electroconvulsive therapy without lasting benefit, and 55 of the patients were receiving maintenence EST once or twice a week prior to being placed on reserpine. It was found that discontinuance of therapy prior to three consecutive months did not give a fair clinical trial and also increased the probability of relapse. In some cases, it was necessary to continue therapy up to six months. The occurrence of the turbulent phase (with exaggeration of symptoms) is *not* an indication for discontinuing treatment. Results of the treatment are summarized in TABLES 4, 5 and 6.

On the admission service[4] (females), 24 markedly disturbed patients were placed on 2 to 3 mg. of oral medication alone. Seven of these patients improved sufficiently to be released from the hospital, and an additional 11 showed definite improvement. Two more showed slight improvement, and only four of the group showed no improvement or became worse. An additional 49 patients were given combined oral and intramuscular treatment, of whom only eight failed to show some degree of improvement. Eleven were sufficiently improved to be considered ready for release, but two relapsed when medication was withdrawn. In the light of subsequent study, this initial work on the admission service is now judged to have been done with the use of inadequate

TABLE 4

SUMMARY OF IMPROVEMENT WITH RESERPINE IN RESPECT TO DIAGNOSIS

Diagnosis	Markedly improved	Moderately improved	Slightly improved	No improvement	Number of cases
Dementia praecox	26 (20.6%)	51 (40.5%)	30 (23.8%)	19 (15.1%)	126
Manic depressive	1 (33.3%)	1 (33.3%)	1 (33.3%)	—	3
Involutional psychosis	1 (14.3%)	5 (71.4%)	—	1 (14.3%)	7
Psychosis with mental deficiency	3 (50.0%)	—	—	3 (50.0%)	6
Epileptic psychosis	—	1 (25.0%)	3 (75.0%)	—	4
Other conditions	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	4
Total	32 (21.3%)	59 (39.3%)	35 (23.3%)	24 (16.0%)	150

TABLE 5

IMPROVEMENT WITH RESERPINE IN RESPECT TO AGE

Age	Markedly improved	Moderately improved	Slightly Improved	No Improvement	Number of Cases
15–20	4 (50.0%)	2 (25.0%)	2 (25.0%)	—	8
21–30	7 (20.6%)	11 (32.4%)	11 (32.4%)	5 (14.7%)	34
31–40	9 (17.6%)	21 (41.2%)	9 (17.6%)	12 (23.5%)	51
41–50	8 (21.1%)	17 (44.7%)	8 (21.1%)	5 (13.2%)	38
51–60	2 (16.7%)	6 (50.0%)	4 (33.3%)	—	12
61–65	2 (28.6%)	2 (28.6%)	1 (14.3%)	2 (28.6%)	7
					150

TABLE 6

IMPROVEMENT IN RESPECT TO DURATION OF ILLNESS AS MEASURED FROM TIME OF FIRST HOSPITALIZATION

Duration of illness from first hospitalization	Markedly improved	Moderately improved	Slightly improved	No improvement	Number of cases
Less than 2 years	7 (46.7%)	4 (2.67%)	3 (20.0%)	1 (6.7%)	15
2 to 4 years	8 (36.4%)	10 (45.5%)	2 (9.1%)	2 (9.1%)	22
4 to 10 years	9 (15.2%)	24 (40.7%)	15 (25.4%)	11 (18.6%)	59
More than 10 years	8 (14.8%)	21 (38.9%)	15 (27.8%)	10 (18.5%)	54
					150

courses of treatment. The drug, at that time, had been used primarily as a sedative to hold the patients until the permits and work-ups for electroshock could be obtained. In this group of 49 patients, 17 who had been scheduled to receive electroshock were adjudged so improved that the treatment was not given.* As a result of these preliminary studies, the results were felt to be sufficiently encouraging to use this form of therapy on as many new female admissions as possible. Since Dec. 1, 1954, only occasional patients have been given shock when the number on reserpine has become too large for the careful study we are requiring for each patient in this study. As a result of

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* Final review showed that in 54 of 80 patients originally scheduled for shock treatment, the EST was not necessary because of prior reserpine therapy.

TABLE 7

RESULTS OF RESERPINE THERAPY ON MALE ADOLESCENTS

	No. of cases	On combined oral & i.m.		On oral following combined		Postmedication	
		Improved	Unimproved	Improved	Unimproved	Improved	Unimproved
Schizophrenics	11	11	0	3	8	1	10
Nonschizophrenics	14	14	0	10	4	8*	6

* Ready for release.

another study, complete data on the results of shock on the same service for the previous six months are available for comparison, as are the results on the male reception service where shock is still being used. Since the admission rate to this hospital is in excess of 2000 patients a year, quite definitive results should be available at the end of this time.

In a group of disturbed adolescents, all of the patients improved markedly as long as they were continued on medication. Only one of the 11 schizophrenic adolescents maintained improvement when medication was withdrawn. Of 15 nonschizophrenic adolescents, one ran away from the hospital before evaluation could be completed but, of the remaining 14, eight have maintained their improvement from two to five months and are considered ready for release from the hospital as soon as suitable placement can be arranged for them. Details of this study were reported at the Regional Research Conference of the American Psychiatric Association held in Galveston, Texas.[5] For details, see TABLE 7.

We are extremely interested in how results with chlorpromazine compare with those on reserpine[6] and whether there may not be factors which indicate, in certain conditions, whether the one drug is preferable to the other. To this end, we are currently doing a study of 240 patients, 80 each of which are on placebo, chlorpromazine, or reserpine. The first phase of this study has been completed, and now patients who have failed on the one medication are being tried on the alternate one. Results are not yet available for comment.

A percentage of the patients who fail on the first course of reserpine do respond on the second course and, combining chlorpromazine and reserpine,[7] as is currently being done with about 300 patients, offers another extremely promising avenue of approach.

At recent meetings of the American Association for the Advancement of Science,[8] one of the authors had the opportunity to listen to the experiences of a considerable number of other investigators, some of whom did not obtain such satisfactory results. It would seem that failures were due to one of two factors: either the dosage was inadequate, or there was failure to recognize the turbulent phase of treatment, so that when the patient's symptoms became aggravated (as is normally expected), treatment was discontinued.

The side reactions have all been reversible. Nasal stuffiness, tremulousness, and mild gastrointestinal disturbances are extremely common. Drowsiness, feelings of fatigue, and increased salivation are less frequent. In occasional patients, there is edema of the face and feet, and unusual sensations in the muscles. These side effects almost invariably disappear within the first two or three weeks of treatment. In a few patients, there were convulsions, but these attacks were limited to one or, at the most, two seizures, and did not occur after the early stage of treatment.

Later in the course of treatment, about 5 per cent of the patients developed typical Parkinsonism, which disappeared on reduction of dosage. Our general attitude has been to press treatment despite Parkinsonian symptoms until the patient appears either on the road to recovery or gives evidence that a good response is unlikely. There is one other side effect for which it is wise to be alert; namely, that an over-dosage of reserpine will cause a typical toxic reaction with confusion and loss of appetite. In these cases, obviously, dosage should be reduced.

In addition, there have been individual successes with such conditions as stuttering, and one very dramatic response in a physician who suffered from Huntington's chorea.[9] The specific percentage of success to be expected in particular diagnostic categories is something which we expect to clarify further during the coming year. If the percentage of discharges obtained to date holds up for the larger number of patients now being treated, there is little question that the drug will prove a tremendous economy. The course of treatment for an individual patient costs approximately $30 and, in view of discharges which would not otherwise occur and the reduction in need for specialized personnel (which includes the freeing of some doctors who were formerly necessary to administer electroshock and insulin), there is no question but that the drug would be a boon to psychiatry. It appears probable that it will shorten the duration of hospitalization economically, and will permit the discharge of patients formerly deemed unmovable, and we already know that it serves to make more comfortable those patients who must remain hospitalized. It would seem that the next major field for exploration would be to determine whether use of the drug might not serve to prevent the number of patients requiring admission to mental hospitals.

Because the physician treating such patients can become oversanguine, a careful "informal" check was made by one of us (AMS) throughout the hospital among the nurses and attendants. Many of these employees are old-timers and, since they have to live with the patients day by day, they are apt to be more conservative in their evaluation of beneficial effects. These employees were firmly convinced that reserpine did make the patients definitely quieter, and they were equally convinced that there were less assaults, arguments, and disturbances in the wards. Many of the patients had been known to this author for years, and most of those on medication asserted that it gave them the feeling of being less tense. Their self-evaluation was that they were definitely improved. All of this information, of course, does not permit tabulation in statistical form. Evaluation of this type does serve to confirm the tables and charts gathered on a less personal basis and, when both point in the same direction, there is reasonable assurance that the drug is fulfilling an extremely useful function and has real promise of value for the future.

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TREATMENT OF CHRONIC SCHIZOPHRENIC REACTIONS WITH RESERPINE*

By Leo E. Hollister, George E. Krieger, Alan Kringel, and Richard H. Roberts
Stanford University School of Medicine, San Francisco, Calif., and Veterans Administration Hospital, Palo Alto, Calif.

An introduction to the usefulness of reserpine (Serpasil) in neuropsychiatry seems hardly necessary at this time, even though the first American report was read only one year ago before this very Academy.[1] At that time, we had had some experience with the alkaloid in patients with hypertension but little in the mentally ill. Meanwhile, many investigators have studied the drug intensively, and several reports, including our own,[2] have already been made.

We purposely chose patients with chronic schizophrenic reactions for evaluation, because this particular diagnostic category accounts for 47 per cent of mental hospital in-patients. Each year, at least $235,000,000 is spent caring for this group of 270,000, whose average hospitalization lasts 13 years—usually during the most productive period of life. In terms of human misery, the cost of this illness is incalculable.

Eight years ago, an analogous situation existed in patients with tuberculosis. Since the introduction of effective drugs in the treatment of that disease, the entire character of the treatment has changed. The necessity for hospital treatment of tuberculosis has diminished. The duration of hospital stay has been shortened. The degree of disability has been lessened, and the mortality rate has been reduced. It is altogether possible that reserpine, chlorpromazine, and other drugs to follow, may cause a similar revolution in the treatment of the mentally ill.

Method of Study

One hundred twenty-seven patients hospitalized with chronic schizophrenic reactions were selected for treatment with reserpine. The schizophrenic reactions were classified as paranoid in 62 patients, catatonic in 27, hebephrenic in 19, and other types in 19. All but 5 patients were men. The age of the patients ranged from 21 to 76 years, the median being 32. These patients had been ill for periods varying from 6 months to 37 years. More than half had been ill for more than 9 years. One hundred twelve of the patients had received electroconvulsive and/or insulin-shock therapy; 13 had undergone bilateral prefrontal leucotomy. The main reasons these patients were selected for treatment were these: (1) they were so disturbed as to require frequent restraint, seclusion, or heavy sedation; (2) they were too anxious or hostile or too withdrawn and uncommunicative to be amenable to other psychiatric treatment; (3) they had not responded to any previous therapy.

In the initial pilot study, a daily oral dose of 1 mg. of reserpine was used. The amount of change noted in patients from this dose was not great. Next a double-blind study was made to determine the effectiveness of daily doses of

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* The authors wish to thank the many nurses and hospital aides whose patience and persistence facilitated the treatment of these patients.

2 mg. of reserpine orally. Nineteen patients received this dose of reserpine daily for 50 days, and 19 other patients received identical placebos. Six of the 19 patients treated with reserpine showed improvement of unequivocal though not marked degree. Two patients treated with placebos showed improvement. It was noted that the improvement in patients receiving reserpine was, for the most part, limited to a less regressed group. Thus it was concluded that an oral dose of 2 mg. of reserpine daily would not be adequate for the majority of patients with chronic schizophrenic reactions. Patients who had been started on oral dosage were maintained on this form of medication to determine the effect of such doses when given for long periods.

Our first experience with a schedule of combined daily doses of reserpine of 5 mg. parenterally and 3 mg. or more orally produced several outstanding results. It was determined to test this dosage schedule by the double-blind technique. Twenty patients were treated with 5 mg. doses of reserpine intramuscularly for 7 days, with an oral daily dose of 3 mg. being added on the third day and continued thereafter. Thirteen of these 20 patients showed improvement when an evaluation was made during the third week of such treatment. Only 3 of 20 patients treated in a like manner with placebos showed improvement. It was decided to use a combined parenteral-oral dosage schedule for most of the patients to be treated subsequently.

Criteria for judging improvement had to be flexible because of the considerable variations in the symptoms and severity of illness among individual patients. Therefore, a given degree of improvement might have different meanings in absolute terms in different patients. In general, patients were considered to have shown slight improvement if they were appreciably less disturbed, required less sedation, seclusion, or restraint, or could be moved to a ward with less severely ill patients. We accorded moderate improvement on the basis of (a) no further requirement of seclusion or restraint and a markedly diminished need for other forms of sedation; (b) improvement in behavior which permitted the patient to participate in activities programs or group and individual psychotherapy; and (c) social improvement which made possible the granting of ground privileges or passes from the hospital for the first time. Marked improvement implied that the patient had made a great change according to the criteria listed above and that he was being considered for release from the hospital.

Judgment of improvement was made clinically by the patient's psychiatrist, acting not only on his own observations, but also on those reported to him by other ward personnel. In addition, during the double-blind studies, the Hospital Adjustment Scale[3] was used to compare with the clinical rating. In general, the results obtained from the use of this scale corroborated the clinical impression. While the scale showed consistency when it was completed by the same observer, usually a hopital aide, there were often differences when other observers reported. These differences were frequently unexplainable on the basis of clinical change. Since it was impossible to assure such consistency of observations, the psychiatrist's opinion, based on multiple sources of information and tempered with his critical judgment, was considered to be paramount.

Table 1

Results of Treatment with Reserpine in 127 Patients with Chronic Schizophrenic Reactions

Result obtained	No. patients
Unimproved	29 (23%)
Slightly improved	40 (32%)
Moderately improved	36 (28%)
Markedly improved	22 (17%)
Total improved—98 (77%)	

Results of Study

Improvement was noted in 98 (77 per cent) of the 127 patients treated with reserpine (TABLE 1). The degree of change was marked in 22 patients, moderate in 36, and slight in 40. No appreciable improvement was noted in 29 patients. At the time these evaluations were made, treatment had been carried out for at least six weeks in the case of patients receiving combined parenteral-oral dosage, and at least eight weeks in those patients who received only oral medication. Some patients had been under continual medication for eight months.

When patients showed marked improvement, the result was frequently astounding, even to psychiatrists of long clinical experience. Patients who had been clearly responding to hallucinations, or careless of personal habits, or hostile, destructive, and resistive, or completely withdrawn and mute became, within a short period of time, clean, cooperative, and communicative persons. Many of the patients who showed moderate improvement were better than they had been during most of their hospital course. In many cases, these patients were able, for the first time, to participate in some of the psychiatric rehabilitative programs which they had previously spurned. Often moderately or markedly improved patients demonstrated some evidence of increased understanding of the nature of their illness and the methods by which it might be treated. Previously insurmountable psychotic defenses often weakened considerably. Hallucinations either disappeared or were no longer troublesome. Slight degrees of improvement were often most appreciated by the hospital staff or the patients' relatives, both of whom were gratified to see these patients become more approachable and show greater interest in their surroundings.

The frequency with which improvement occurred was greater in patients who received a combined parenteral-oral dosage schedule (TABLE 2). Oral doses of 1 to 4 mg. of reserpine daily were given to 44 patients, 27 of whom had received these doses for 5 months or more. Only 13 (30 per cent) of these 44 patients were judged to have shown moderate or marked improvement. A schedule of parenteral doses of 5 mg., and in a few instances 10 mg., daily followed by oral doses of 2 to 8 mg. daily was used in 83 patients, 60 of whom had received such doses for 5 months or less. Forty-five (54 per cent) patients treated in this fashion showed moderate or marked improvement.

The duration of treatment was not so important as the dose of reserpine in the production of a good result. Twenty-four of the 58 patients who showed

TABLE 2

RELATIONSHIP OF DOSAGE SCHEDULE OF RESERPINE TO RESULT OBTAINED FROM TREATMENT OF 127 PATIENTS WITH CHRONIC SCHIZOPHRENIC REACTIONS

Dosage schedule	No. patients	Moderate or marked improvement
Oral dose (1–4 mg./day)	44	13 (30%)
Parenteral-oral dose (5 mg. i.m., 2 to 8 mg./day orally)	83	45 (54%)

TABLE 3

RELATIONSHIP OF DURATION OF ILLNESS TO RESULT OBTAINED FROM TREATMENT WITH RESERPINE IN 127 PATIENTS WITH CHRONIC SCHIZOPHRENIC REACTIONS

Duration illness	No change	Slightly improved	Moderately improved	Markedly improved	Total (moderate or marked improvement)
½ to 2 yrs.	1	2	6	6	15 (12)
3 to 12 yrs.	21	29	25	16	91 (41)
13 yrs. or more	7	9	5	0	21 (5)
Total	29	40	36	22	127

moderate or marked improvement had been treated 3 months or less. Most of the remaining 34 patients had shown much of their improvement during the same period. On the other hand, 14 of the 29 patients who had not shown any kind of improvement had been treated for 4 months or more. Although there may be increasing improvement with prolonged administration of reserpine, it is probable that such improvement is due not solely to the drug but also to the greater amenability of the patient to psychotherapeutic rehabilitative measures.

It appears that the duration of the patient's illness is important in predicting the results of treatment (TABLE 3). Moderate or marked improvement was noted in 12 of 15 patients whose illness was two years or less in duration. Even in patients whose illness began as long ago as World War II (up to 13 years in duration), 41 of 91 patients showed such improvement. However, only 5 of 21 patients who had been ill for a longer period showed moderate improvement, and no patient in this group manifested marked improvement.

The type of schizophrenic reaction least benefited from treatment was the hebephrenic (TABLE 4). Even when one considers only patients treated with combined parenteral-oral doses, the results were poorer in the hebephrenic group. Reactions of paranoid and catatonic type responded equally well to the same dosage schedule. Results were comparable in the group composed of mixed or unclassified types of reaction.

Five patients were released from the hospital following treatment with

TABLE 4

RELATIONSHIP OF TYPE OF SCHIZOPHRENIC REACTION TO RESULT OBTAINED FROM TREATMENT WITH RESERPINE IN 127 PATIENTS WITH CHRONIC SCHIZOPHRENIC REACTIONS

Type of reaction	No change	Slightly improved	Moderately improved	Markedly improved	Total (moderate or marked improvement)
Paranoid	11	19	24	8	62 (32)
Catatonic	7	7	5	8	27 (13)
Hebephrenic	7	8	2	2	19 (4)
Others	4	6	5	4	19 (9)

reserpine. Twenty other patients were allowed to leave the hospital for varying periods of time. Since the group of patients selected for treatment with reserpine was not an accurate sample of the entire hospital population (being for the most part less favorable candidates for therapy), no comparable statistics are available concerning discharge rates in this group. However, the course of these patients prior to treatment with reserpine gave no indication that they would be ready so soon for release from the hospital.

Four patients who had been scheduled for leucotomy were not operated on because of their favorable response to reserpine. At least 10 other patients would have been considered for leucotomy had their course not been changed by the drug. A number of patients were managed through periods of disturbed behavior by use of reserpine rather than electroconvulsive therapy. Only 2 of the 83 patients in this series who received combined parenteral-oral doses of reserpine were given electroconvulsive therapy after the drug was started. This represents a substantial decrease in the amount of electroconvulsive therapy which would ordinarily have been given these patients.

Side-effects led to the stopping of treatment in only one patient. This man had an exacerbation of vasomotor rhinitis and bronchial asthma. All other adverse effects were managed by alterations in the program of treatment. In this group of patients, virtually all the noticeable side-effects occurred in patients treated with parenteral doses of the drug (TABLE 5).

The most prominent nervous system reaction was sedation. After the first parenteral dose of reserpine, most patients became listless and some appeared to be asleep, though easily aroused. Soon, this effect abated with no lessening of dose. At the dosage level used in this study, only occasionally did patients exhibit a paradoxic response of increased agitation and restlessness. Most such responses were interpreted as temporary discharges of emotional tension. Only one patient with a schizophrenic reaction became considerably depressed while on the drug. Tremor and shivering were frequently seen, but the Parkinson syndrome was not produced in any patient at this level of dosage. Gen-

TABLE 5

SIDE EFFECTS OF CONSEQUENCE IN 127 PATIENTS WITH CHRONIC SCHIZOPHRENIC REACTIONS TREATED WITH RESERPINE

Effect	No. patients
Hypotension and/or bradycardia	10
Syncope	3
Reactivation of duodenal ulcer	2
Vomiting of unknown cause	1
Aggravation of vasomotor rhinitis and bronchial asthma	1*
Depression	1

* This patient was dropped from treatment.

eralized flushing, injection of the conjunctivae and nasal mucous membrane, and excessive salivation were autonomic effects frequently observed.

Cardiovascular effects, such as a fall in blood pressure and slowing of the pulse rate, were frequently present. These vital signs, however, went below physiologic limits in only 10 patients. Three of these patients had syncopal attacks during the initial stage of hypotension and bradycardia. Rest in bed and dividing the doses of parenteral medication met this problem. A few patients had transient premature cardiac contractions. One patient briefly developed a prolongation of the auriculoventricular conduction time. Another patient, with electrocardiographic evidence of bundle branch block of several months' duration prior to reserpine, showed a reversion to normal intraventricular conduction time while receiving the alkaloid.

It has been pointed out that reserpine alters sympathetic-parasympathetic balance by partial suppression of the sympathetic side of the autonomic nervous system.[4] Thus, side reactions of reserpine mimic changes produced by parasympathetic stimulants. Theoretically, individuals with duodenal ulcer, bronchial asthma, and certain other conditions might be made worse by the alkaloid. Though one patient with bronchial asthma was dropped from treatment, it was primarily because of increased nasal symptoms. Nothing in his case suggested the development of an intractable asthma. Two patients with a history of duodenal ulcer had reactivation of their symptoms while under treatment with reserpine. Neither patient had been on an active ulcer regimen. When such treatment was started, both responded satisfactorily. One patient developed intractable vomiting without any demonstrable abnormality. He responded to the temporary addition of chlorpromazine to his schedule of treatment. None of our patients had an allergic rhinitis. In those patients with nasal obstruction, symptomatic treatment sufficed to produce adequate relief except in one case. No patient in this series had an ulcerative colitis or irritable colon. When diarrhea occurred, the symptoms were relieved by use of anticholinergic drugs.

Comments

The introduction of reserpine represents a significant advance in psychiatric medicine. Reports from others confirm the encouraging results we have had.[5] By use of double-blind methods of testing, by selection of patients difficult to treat, by setting up definite standards for improvement, and by adopting a conservative and critical attitude toward this study, we believe we have avoided the pitfall of over-enthusiasm. Nevertheless, many who came to scoff at this drug stayed to praise it.

The results reported in this study do not represent the best that might be obtained with the drug. First, the majority of the patients selected for treatment did not appear to be promising candidates for any kind of therapy. Many of them had been treated with previous somatic therapy or leucotomy, and these measures had failed to help them. Furthermore, if the patient was not especially disturbed, or if he was actively participating in the psychotherapeutic program of the hospital, he was not likely to be chosen for treatment with reserpine. Second, because this study covers the period during which we were learning how to use this drug, it is obvious that some patients did not receive adequate treatment. As we now know more about the correct use of reserpine, results from treatment should become better.

Until there is more definite knowledge concerning the mode of action of reserpine we prefer to think of it primarily as a sedative. Unlike previous sedatives, its effect is produced without clouding of consciousness or impairment of motor function. Thus, reserpine can be used to produce a degree of sedation without somnolence in psychiatric patients far beyond that ever before attained. The drug appears to put a brake on the momentum of the psychotic process, allowing the patient to drop some of his psychotic defenses. It is during this period that he may learn that there are other, better ways to deal with his problems. In most patients, this learning process requires the energetic assistance of the psychiatrist and other hospital personnel.

Conclusions regarding the best selection of patients for treatment with reserpine are not yet definitive. While there seems to be not a single contraindication to the use of the drug, most physicians will want to use it as effectively as possible. The drug certainly appears to be indicated for patients who exhibit excessive emotional tension and anxiety. It would also appear that reserpine may be most effective in patients whose schizophrenic reaction is of relatively short duration. In many patients with acute schizophrenic reactions or milder forms of chronic schizophrenic reactions, use of this drug may shorten or prevent hospitalization. Patients who have been psychotic for prolonged periods or those patients who show marked mental and behavioral deterioration may not be expected to improve as frequently or as markedly as patients who show less change. The hospital adjustment of such patients, however, may be improved to a considerable degree.

It is now clear that the dose of reserpine is of critical importance in determining the result obtained. To a great extent, the dose required is an individual matter for each patient. The optimal level of dosage appears to be proportional to the intensity of the emotional disturbance. We feel that most patients with chronic schizophrenic reactions require initiation of treatment with parenteral doses of at least 5 mg. of reserpine and continued daily doses of 2 to 8 mg. orally. There is the possibility that some patients who do not respond to such a dosage schedule might be helped by prolonged or augmented parenteral doses, or by combined treatment with chlorpromazine and reserpine.[6] Other possible combinations that might be helpful include the use of conventional sedatives or, in some patients, stimulants in connection with reserpine.

Two problems arise concerning the duration of treatment. First, how long should treatment be continued to provide an adequate trial? Second, when should treatment be stopped in the patient who has improved? At the moment, we consider that an adequate trial of reserpine consists of three months of treatment beginning with a relatively high level of dosage. So far, the solution of the problem of when to stop treatment has been empiric. We are convinced that lasting improvement from treatment with reserpine is dependent not only on how much or how long the drug has been given, but also on what has happened to the patient while he is on the drug Thus, we regard the relapse of a patient in whom the drug is discontinued as a manifestation of our failure to exploit fully the therapeutic opportunity the drug has provided. Since the evolution of a psychosis is generally a long process, it seems reasonable to believe that its resolution might also be protracted. Much needs to be undone before the patient will be well.

Since the use of reserpine in psychiatry is a form of somatic therapy, its relation to other somatic therapies should be considered. The fact that several of our patients have thus far been spared leucotomy by its use would indicate that leucotomy may be less often required in the future. We feel that all leucotomy candidates should have a therapeutic trial with reserpine prior to surgery. Convulsive or shock therapies may be needed less frequently with the advent of reserpine. For controlling disturbed behavior in chronic schizophrenics, reserpine is at least the equal of electroconvulsive therapy. The possibility exists that some advantage may be gained from the combined use of reserpine and electroconvulsive therapy.[7]

Reserpine unquestionably represents a most valuable adjunct in the treatment of patients with chronic schizophrenic reactions by psychotherapeutic procedures. The great difficulty in the use of psychotherapy with these patients has been the fact that so many cannot be reached by it, even with the most painstaking and patient endeavor. It is now possible to create, in a significant number of these patients, such therapeutic opportunities. Thus, treatment with reserpine often represents, not the beginning of the end of therapy, but the end of the beginning. There is no competition between the use of reserpine in psychiatry and the application of psychotherapeutic techniques. Rather, they complement one another. Although the use of reserpine may stimulate increased efforts in providing psychotherapy for these patients, it is certainly true that, henceforth, such efforts will be far more rewarding than ever before.

Summary

One hundred twenty-seven patients hospitalized with chronic schizophrenic reactions were treated with reserpine for one to eight months. The majority of these patients had been ill for nine years or more. In 98 patients, significant improvement was noted, this being moderate to marked in 58. Twenty patients were able to be granted passes from the hospital. Five were discharged.

Improvement was characterized by decreased tension, hostility, aggressiveness, delusions, and hallucinations, and by increased sociability and amenability to other psychiatric treatment.

The majority of patients with chronic schizophrenic reactions require initiation of therapy with parenteral doses of five mg. daily and maintenance doses of two to eight mg. orally each day. A relatively high percentage (54 per cent) of patients treated in this fashion showed moderate or marked improvement. Duration of treatment is less important than dosage level. The shorter the duration of the illness, the more likely a good result will be obtained.

Complications of therapy were slight. Treatment was discontinued in only one patient. Four patients in this series had been scheduled for leucotomy, but were not operated on because of favorable response to the drug. A number of other patients were managed through periods of disturbed behavior by use of reserpine rather than by electroconvulsive therapy. The need for leucotomy and the convulsive therapies may decrease with increased and proper use of reserpine.

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TREATMENT OF RESERPINE-INDUCED DEPRESSION WITH A NEW ANALEPTIC: PHENIDYLATE*

By John T. Ferguson
Traverse City State Hospital, Traverse City, Mich.

Reports have appeared recently concerning induced depression and excessive drowsiness in patients taking varying doses of reserpine. We, too, have encountered this situation, in some instances, in a series of approximately 500 patients who have been on reserpine for about six months. To a large extent, however, this condition is no longer a problem at our institution, since it has proved amenable to a new compound which we have been studying clinically. This new drug, phenidylate—phenyl-(α-piperidyl)-acetic acid methyl ester (Ritalin)—is a synthetic preparation which could be described as a psychoanaleptic, a mental and physical stimulator which, in addition to having these properties, seems to counterbalance the reserpine-depressing activity. It seems to arouse the apathetic patient to mental and physical activity without causing any significant side reactions.

In the course of our study with phenidylate, we felt the good clinical results obtained with the drug as a "mental awakener" warranted its use on several cases of reserpine-induced depression. We found that administration of phenidylate to these patients appeared to overcome the depression and clear the drowsiness sufficiently to permit an awakening-to-reality and some physician-patient contact. The purpose of the present paper, primarily, is to present some preliminary results we have obtained with this new compound on our chronic, regressed, negativistic patients, using it alone or in combination with reserpine.

The need for a general analeptic agent to control the behavior of these patients has been recognized for some time. A variety of drugs has been tried in an effort to meet this need. Notable examples of such agents include amphetamine sulfate,[1] caffeine sodium benzoate,[2] metrazol,[3] methamphetamine hydrochloride,[4] isoniazid,[5] and stimulating barbiturates.[6] None of these is entirely satisfactory, and some have been too toxic for continued use. It was this problem which led us to consider phenidylate.

Animal studies demonstrated that this drug has the typical central stimulating effects of the phenylisopropylamine derivatives, with the addition of a stimulating caffeinelike effect. However, phenidylate differed from the psychomotor amines by being milder in peripheral sympathomimetic effect and in the quality of its psychomotor action. It lacked the marked euphorizing tendency of these drugs and, in therapeutic doses, was completely free of undesirable side reactions. Moreover, despite its caffeine-like action, it did not produce the usual complex circulatory reactions associated with this drug.

Meier, *et al.*[7] found that phenidylate produced mental stimulation and a coordinated increase in motility in the rat, dog, mouse, and rabbit. In their opinion, the intensity of action lies somewhere between amphetamine and caffeine.

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* Both reserpine (Serpasil) and phenidylate (Ritalin) used in this study were supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Their experiments showed that, depending on the animal, species, and mode of administration, the central stimulating effect appeared after doses of 0.5 to 1.5 mg./kg., lasted for several hours, and then subsided, leaving the animal treated with signs of fatigue. Larger doses produced an atactic gait and clonic-tonic convulsions. The drug also showed a marked antagonism to certain depressants, *i.e.*, diethylbarbituric acid, ethylphenylbarbituric acid, Pentothal, chloral hydrate, and urethane. It stimulated respiration, particularly when the respiratory center was previously inhibited by morphinelike substances, caused a moderate rise in blood pressure, and increased the heart rate without producing any marked peripheral sympathomimetic effects.

In Europe, Drassdo and Schmidt[8] studied the effect of phenidylate on the mental capacity and psychic mood of human volunteers. Ten persons were given phenobarbital to produce mental sluggishness and were then required to perform simple arithmetical calculations. The subjects were timed for their performance. After a 14-day interval, the same volunteers were given phenidylate (20 mg.) with phenobarbital, and were again timed for their performance. The results of the study showed a definite increase in mental capacity and alacrity with phenidylate. In performing subtractions, the increase in capacity ranged from 10.5 per cent to 92 per cent. One volunteer registered as much as a 330 per cent increase. In the performance of the easy calculations, the subjects with phenidylate showed an increase in mental capacity of 11.5 per cent to 53 per cent.

Psychic effects of the drug were determined by subjectivity or the personal observations of the investigators. Thirty-two reported a "good mood," 12 were slightly stimulated, 12 found no activation, and 4 reacted negatively with headache, perspiration, and anginal complaints. Of the 60 persons tested, about 70 per cent reported a pleasantly stimulating effect with phenidylate.

Before initiating our study, a pilot group of 10 catatonics was given 10 mg. of phenidylate a day. The second day, one of the patients who used to tie her dress in knots had stopped doing it. Another, who never spontaneously moved out of her chair, arose to go to the bathroom. A third, who had to be pulled into line to eat, stood in line voluntarily the second day.

In general, the majority seemed brighter, shook hands, and even came to the office when called. It was our considered opinion that such results warranted a clinical trial.

The patients reported in this study totaled 68 and ranged in age from 24 to 71, with a hospital stay of 3 to 52 years. They were selected from 15 wards, each ward consisting of different behavior patterns. Dosages were individualized and ranged from 10 to 40 mg. t. i. d., given at 8:00 A.M., 12:00 A.M., and 4:00 P.M.

Before therapy was initiated, the behavior of each patient was charted according to a Behavior Profile Chart prepared by the author. The chart is broken down into 15 categories: I—Type of ward; II—supervision; III—appearance; IV—aggressiveness; V—motor activity; VI—conversation response; VII—attention; VIII—speech; IX—reaction to rehabilitation; X—

cooperation in routine; XI—socialization; XII—personal care; XIII—feeding XIV—soiling; XV—sleep. Each of these categories is further subdivided and numbered according to the facet of negative or positive behavior, *i.e.*, appearance: bizarre 5; decorative 4; odd 3; overdressed 2; expected dress 1; sloppy (2); partial (3); strong suit (4); stripper (5). Parenthetical numbers are considered negative; 5 either way indicates the worst, while 1 is the best. By means of this chart, a complete individual patient record was maintained throughout the study by the nursing attendants. Behavior changes, if any, were recorded each day of the study. Only those patients who were negative in 12 of the 15 categories were selected for the study.

As of this writing, we have noticed a decrease in the need for helpful supervision. Patients are cleaner and their general appearance is much improved. There has been no increase in aggressiveness beyond the normal. Their attention, conversation, and speech have moved toward normal. The cachectic patients eat better (there has been an average weight gain of eight pounds in the group studied). Their sleep pattern has remained normal and there has been a marked decrease in soiling. We have likewise noted a decided improvement in their ability to cooperate in ward routine and in the rehabilitation program.

The following typical cases are illustrative of what has been achieved with phenidylate alone, and in combination with reserpine.

Case L. T.—Female, hebephrenic, age 71, admitted April 14, 1902. A quiet withdrawn patient that required almost complete care. Chart record before phenidylate. Is on supervised ward. Will move with group if called individually. Partially dressed. Aggressiveness—out of contact. Motionless unless prodded. Conversation—only partial response. Unable to pay attention unless prodded. Speech—talks less than expected. Uninterested in rehabilitation. Doesn't understand about cooperation. Doesn't like to socialize. Patient needs help in personal care, in feeding, and soils occasionally. Sleeps through the night.

Phenidylate, January 13, 30 mg. t. i. d. More alert. Started eating by self today.

January 17. More talkative. Writing letter. Goes to dining room. Eats by self, normally. Much more cooperative. Good on routine. Has stopped sitting around.

January 21. Helping in dining room with dishes. Continues a slow, steady improvement.

January 25. Continues to be of help, is cooperative. Eats much more.

January 27. Dresses. Aggression and motor activity normal. Some slow overplay but remarkably improved.

January 31. Continues as if slowly waking. Asks to help in dining room, but eats all the time.

Case M. W.—Female, mental defective, age 25, admitted July 15, 1951. Spits saliva into front of blouse at regular intervals, always soaked. Kicks left foot steadily at intervals and seems to spit in rhythm with foot movements. Unless prevented, will always put clothes on backwards. Chart record before phenidylate: on a supervised ward. Watchful; moves when others move.

Partially dressed. Hides. Motionless. Conversation suspicious, answers questions slowly. Preoccupied, no attention. Talks only when prodded. Makes effort to rehabilitate. Fair routine cooperation. Won't mix. Needs supervision in dress. Messy eater. No soiling. Normal sleep.

Phenidylate, January 11, 30 mg. t. i. d. Went to dining room with group and ate normally. Moved out of chair, less spitting.

January 12. More active and alert. Talking.

January 13. Out of chair more. Spitting almost stopped. Came to nurse's office and asked nurse to have her social worker come to talk to her. Asleep in bed at 9 P.M. when ward was checked.

January 17. Same as 1/13. Raised dose to 40 mg. t.i.d.

January 20. Has perked up. Started using toothbrush today. More cheerful. Clothing neat. No spitting on clothes.

January 21. Same as 1/20.

January 25. More active. Went off ward to show today. No spitting. Off chair.

January 31. Stopped spitting on clothes. Out of chair. Brushes teeth and combs hair. Easier to handle. Visits only when approached but is friendly then. Reduced phenidylate to 30 mg. t.i.d.

Case B. L. McL.—Female, hebephrenic, age 27, admitted Feb. 3, 1947. Mixed behavior that is good and bad. Cannot go a week without EST. Mannerisms peculiar regarding raising dress. Has some hoarding signs. Quite a problem due to pressure of parents who have no insight to the problem yet are demanding.

Chart record before reserpine and phenidylate: on a supervised ward. Needs extra supervision. Partially dressed. Argumentative, aggressive. Restless. Conversation response excessive. Resists paying attention. Talks most of time. Resists rehabilitation. Resists routine cooperation. Is sociable when opportunity arises. Needs supervision in personal care. Messy or finicky in eating. Does not soil. Light sleeper.

Reserpine, December 18. Started reserpine 0.5 mg. t.i.d.

January 8. Quieter and less active. Some traces of negative signs.

Phenidylate, January 11, add 30 mg. t.i.d., as she is negative.

January 18. Continues more alert but over-all picture is a return to the original negative. However, have been able to keep her off EST (electroshock treatment). More manageable. Still bounces.

January 21. About same as above.

January 23. Raise reserpine to 1.0 mg. t.i.d., as she has become active. Easier to supervise. More cheerful.

January 27. Eats, but is finicky. Anxious about going home. Quieter last day or two. Now goes to occupational therapy. Dressed, but sloppy. Sleeping normally. Holding medicine at 1 mg. reserpine and 30 mg. phenidylate t.i.d.

January 31. Continues at same level. Some anxiety and tension. Reduced phenidylate to 20 mg. t.i.d. Reserpine remaining at 1.0 mg. t.i.d.

Case H. D.—Female, catatonic, age 35, admitted April 17, 1944. Swears. Needs EST to keep activity down. Upset. Chart record before reserpine and phenidylate. On supervised ward. Needs special therapies. Dresses normally. Overaggressive, with spells of temper. Motor activity—retarded, motionless at times. Adequate conversation response. Pays attention. Talks only when necessary. Poor reaction to rehabilitation. Fair cooperation. Socializes. Clean in personal care. Normal feeding. Soils and decorates with excreta. Awakes frequently during the night.

Reserpine, December 15. Started on reserpine 1 mg., t.i.d.

December 20. Has quieted down. Much less supervision. Better sleep. No swearing.

December 30. Much drowsiness. Less in contact. No EST. Swearing again. Negativistic.

Phenidylate, January 10. Ritalin 30 mg. t.i.d. added.

January 14. More alert. No swearing. Still needs help.

January 16. Much improved. Minimal supervision. Does not hide. Responds normally. Ward comments—"Best she has been in years."

January 22. No soiling with help. Sleeps normally. Helps others some. Has shown new spark. Ward comments—"She really has changed." "To think we used to have to treat her every week in order to live with her."

January 24. Quieter. Not as much sex-acting out.

Results and Conclusions

As stated previously, because of the preliminary nature of the study, individualization of dosage was necessary. In most cases, however, the drug's greatest effectiveness appeared after doses of from 20 to 40 mg. t.i.d. The following table indicates the dosage and results obtained with phenidylate on the 68 patients in this study. Fifty-nine, or approximately 87 per cent, showed improvement.

Dose (t.i.d.) *mg.*	No. of Patients	Improved	Unimproved
10	3	2	1
20	1	1	0
30	36	34	2
40	28	22	6
	68	59 (87%)	9 (13%)

Blood and urine studies before, during, and after two months of treatment showed no change. No undesirable reactions to the drug occurred in any of the patients. Pulse and blood pressure remained in the normal ranges. In general, there was little or no increase in motor activity above normal, but a definite and important rise in mental alertness was noted. The patients appeared to be waking up to reality and were more amenable to therapy, suggestion, and social participation. The most responsive patient to phenidylate appears to be the true depressive (negative, withdrawn, dull, listless, apathetic). The response does not seem to have any correlation to age or length of time in the hospital. It is our belief that the drug's action probably lies in the thalamic area, since its effect on the patient is much like that of a lobotomy. We feel that it is still too early to halt the medication in order to determine addiction or habituation. From our observation, however, this dependency factor does not seem to exist.

The second portion of our study, also of a preliminary nature, was an attempt to study the effect of phenidylate on 25 patients who were already on reserpine, but who were affected by such untoward reactions as drowsiness, depression, or "stuffy" nose.

Here, too, the dosages were individualized. They ranged from 0.25 mg. of reserpine and 40 mg. of phenidylate t.i.d. to 5 mg. of reserpine and 10 mg. of phenidylate t.i.d.

In our study, the sleep pattern was our criterion for estimating tension. The further from the normal toward insomnia or other sleepless patterns, the more tense the patient. This was true even if the patient lay motionless on the floor all day.

When patients were given reserpine to the point that supervision, aggressiveness, motor activity, and resistance became negative, drowsiness was usually present. This negativity appeared different from the negativistic attitude found in the normally withdrawn patient. It was actually a form of sleep which, although physically deep, allowed the patient to be aroused easily to some kind of wakefulness and awareness. Thus, reserpine did not make a catatonic stupor out of a catatonic excitement. It appeared to act as a governor over all activity and exerted this force in proportion to the dose given.

When an overactive and/or aggressive patient has been given large doses of reserpine to the point where she spends most of her time sleeping and must be aroused for routine measures, phenidylate may be added to change this picture for the better.

The action of phenidylate does not counteract that of reserpine nor does it oppose the effect of reserpine. The first change noted with the combination seems to be a slow awakening to reality. In most cases, because of the newness of the situation to the patient, there is an element of confusion associated with it. As the patient experiences the progressive change, however, there appears to be an increase in motor activity toward normal. The reaction resembles somewhat that of an electroshock treatment.

The secondary effect of this combined therapy seems to enter many other fields of behavior other than supervision, aggressiveness, motor activity, and cooperation in routine. The patient also shows improvement in appearance, conversation, response attention, reaction to rehabilitation, socialization, and personal care, if these were not normal to begin with.

Our initial dose was approximately 10 mg. of phenidylate t.i.d. for 24 to 36 hours. The amount of reserpine and/or phenidylate was then adjusted as indicated by the patient's behavior. Ten mg. of phenidylate t.i.d. appeared best in our study. The dose of reserpine in these patients could be adjusted downward to one fourth of that originally given.

Cases B. L. McL. and H. D. are representative of the results of treatment with reserpine and phenidylate combination on 25 patients. Of these 25, twenty-two were considered improved. Some have even been sent home.

We found that a resistive patient takes more reserpine than a tense patient, even if both are outwardly negative. Those with recorded behavior patterns that are mixed do better on both drugs than on either drug separately, regardless of their outward predominant behavior pattern.

In our opinion, phenidylate is well worth further clinical trial as an analeptic, particularly in the chronic, regressed, negativistic psychotics—the "specialing" groups who are such an overwhelming maintenance burden on the hospital and community. Also, as stated earlier, phenidylate negates reserpine-induced side reactions, notably drowsiness and "stuffy" nose during chronic treatment of these patients.

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THE USE OF RESERPINE IN SHOCK-REVERSIBLE PATIENTS AND SHOCK-RESISTANT PATIENTS*

By Dean C. Tasher and Marianne Wallenberg Chermak
Manteno State Hospital, Manteno, Ill.

The problems of a large mental hospital subserving the needs of the Chicago metropolitan area are indeed varied. At least one third of the admissions to the Manteno State Hospital, which now averages an 8200 inpatient population, are over 65 years of age and diagnosable as chronic brain syndromes due to arteriosclerosis, senile brain disease, or other illnesses not pertinent to this paper.

The nonschizophrenic remainder of the hospital population consists of mental defectives with psychotic reactions, psychoneurotics, alcoholics, epileptics, and other neurological problems. The most recent breakdown of the census showed that about 47 per cent of the resident population was classifiable as schizophrenic in some form, having a long-term prognosis for continued institutional care.

It is apparent, then, that one of the chief goals of each inquisitive institutional psychiatrist should be that of attempting to alleviate, to some degree, the problem of adequately treating the increasingly large numbers of such chronically hospitalized wards of the state. To this end, various methods of therapy have been tried. At our institution, all the types of standard therapy have been used, with the usual variable degree of success.

On the acute female intensive treatment service, nearly one half of the admitted patients were discharged from the hospital through the use of electroshock therapy, insulin coma therapy, psychotherapy, recreational-occupational-industrial therapy, or any combination of these methods. The usual rate of spontaneous remissions has been observed.

In February 1953, a program was established to determine whether certain female patients with chronic schizophrenic reactions, who had not responded on the acute treatment service and had been relegated to the appropriate chronic cottages, could maintain a continuing contact with reality through the use of prolonged maintenance electroshock therapy. A total of 337 patients were treated with long courses (50 to 200) electroshock treatments over a period of about 18 months, with the result that about 16 per cent were discharged from the hospital. The remainder were divided into two groups, "shock-reversible" and "shock-resistant." The group designated as "shock-reversible," about 90 in all, were those patients who could maintain some degree of reality contact through the usage of one or two treatments per week, but who reversed readily to a psychotic state without such aid. It was repeatedly observed that the individual time of "slippage" in this type of patient averaged from 7 to 14 days without treatment. The ward on which these patients resided was noted for frequent assaults, moderate to very severe injuries, and daily transfers to the hydrotherapy division. By the beginning of last year, it was deemed necessary to project construction plans for hydrotherapy facilities on the ward because of the frequency of violent disturbances. Overcrowding and inadequate numbers of personnel presented insurmountable hurdle to the realization of any further attempt to expand or even to continue long the maintenance shock ward. Therefore, we were on the alert for any type of easily administered efficacious mass therapy which could supplant this program.

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* All of the reserpine (Serpasil) used in this study was supplied through the courtesy of Doctors Jock Graeme and Frank Travers, Ciba Pharmaceutical Products, Inc., Summit, N. J.

Early this summer, when reserpine was made available to us, it was decided to try the most disturbed of these "shock-reversible" patients on drug therapy alone.

The primary aim of the project was to determine, by treating a representative cross section of the schizophrenic population, how many such patients could achieve social recovery and be discharged from the hospital, under outpatient clinic supervision.

Evaluations of all patients reported upon in this paper were made initially, and, from time to time, by each of the authors independently. In the case of those not discharged from the hospital, a final psychiatric evaluation was made during the middle of January 1955. None of the patients received any psychotherapeutic assistance during the period of reserpine therapy other than the usual contact with attendants, psychiatric aides, and the treatment physician to whom they had been accustomed for many months or years. A deliberate effort was made to keep the patients from feeling, in any way, that they were undergoing any "special" form of treatment. This situation was fortuitously aided by the coincidence that the entire hospital population was receiving immunizations against influenza throughout most of the period covered. Not until the patient was ready for discharge was the therapy explained to the patient. At that time, full explanation and plans for maintenance treatment with the medication were outlined to the patient and the relatives. An initial clinic appointment was made, and the details of the one-year conditional release were explained by the Social Service Department.

Use of Reserpine in "Shock-Reversible" Patients

Group I. A group of 22 "shock-reversible" chronic schizophrenic female patients, who were receiving one or two maintenance electroshock treatments weekly, were selected. Approximately one half of this group tended to relapse in from 7 to 15 days after missing their regular treatment into severely withdrawn, anorectic, nearly mute states. Upon being placed back on electroshock therapy, they would regain their former partial contact with reality. Most were somewhat confused as to recent events, presumably due to the electroshock therapy.

The other half were selected because of their tendencies toward assaultive, destructive, and, at times, nearly uncontrollable behavioral outbursts. These patients, through regular maintenance electroshock therapy, were kept in a semblance of control. However, frequent courses of hydrotherapy, increased supervision, and moderately heavy sedation were necessary aids to this therapy.

This group of 22 women, ranging in age from 27 to 50 years of age, had been currently hospitalized from 1 to 6 years. The longitudinal history of most of these patients included many hospitalizations, since the first breakdown had occurred in the late teens or early twenties. All of these were abruptly discontinued from electroshock treatment and started on reserpine on July 20, 1954. Routine urinalyses and blood counts were made and a physical examination confirmed the absence of organic disease in all the subjects, excepting for a mild hypertension of 165/110 in the 50 year old woman. Weights, blood pressures, and pulse rates were recorded by one of us at weekly intervals on all of the patients described in this paper.

In this first group, daily intramuscular injections were given for a period of 30 days. At first, a daily dosage of 5 mgm. was attempted, but this proved to be excessive, particularly in the smaller-sized patients, and was of necessity individually adjusted downward or upward day by day within the limits of the patient's tolerance. All patients were urged to stay in the day room, but if the attendants observed too great evidence of staggering gait, trembling, or dizziness on the part of any patient, they allowed her to recline in the dormitory for an hour or two to prevent injuries from falling.

The usual side effects, noted by others, such as nasal stuffiness, drowsiness, flusing, trembling, conjunctival injection, and mild diarrhea, were observed in about 40 per cent of these patients, usually within an hour or two of the daily injection. No medication was prescribed for any of these minor side reactions and, after the second week of therapy, these symptoms disappeared. Occasionally, partial Parkinsonian syndromes appeared, but were evanescent.

No serious side reactions were observed in this group, although prolonged bradycardia and hypotension caused two of these women to be placed on the acute hospital for overnight observation. The omission of the succeeding day's dose brought prompt restoration of circulatory balance. The effects on blood pressure throughout the seven months' observation period on this group have been repeated in the other groups—namely, that normotensive patients show an initial drop in blood pressure of from 15 to 20 points, both systolic and diastolic, during the first week to 10 days with these relatively high doses. The pulse, frequently rather rapid, due to the high anxiety level of the patient, slows to a definite extent, even to bradycrotic levels of 50/min. or less. When this occurred, dosages were halved or even omitted for a day. By the end of the second week of therapy, most of these physical circulatory phenomena had reverted to their previous levels.

Patients who exhibited the so-called hypotensive blood pressures, not uncommonly found in the chronic schizophrenic, usually tended to develop a more normotensive level after a few weeks' therapy. The one case of mild hypertension returned to a normotensive level in three weeks.

Increased appetite, to the point of a true polyphagia was nearly universal. Weight gains of 10 pounds in two weeks were common and maintained.

Menses, which had been absent in about 50 per cent of the chronic electroshock patients, resumed within a week or two of reserpine therapy.

While these physical effects were being observed, numerous psychiatric phenomena were also apparently taking place. A fairly common characteristic observed was a desire to talk, even though in a psychotic fashion, on the part of patients who had been hostile, evasive, or even mute for many months or years. This amounted to almost a manic press in some instances. Vivid dreams, not unpleasant in content, were reported to the examiner, especially throughout the first month. Two of the middle-aged women developed definite delusions of pregnancy—the one to the point that she complained of labor pains for nearly three weeks, then abruptly announced that she would like an industrial assignment, as her pregnancy had obviously been fallacious. This wish was promptly fulfilled by the activities therapist. It should be mentioned that none of these 22 patients previously had been able to hold an industrial assignment.

At the end of the first month, the patients were changed over to oral medication in a five-day transitional period. Doses then were from 2 to 4 mgm., given each night at bedtime. By the end of the second month, these doses had been reduced to 0.5 to 2.0 mgm. per day orally.

At the end of 10 weeks, the first patient of this group was deemed ready for conditional discharge. This 36-year-old woman had been in and out of various state hospitals for the past 10 years, had been subject to auditory hallucinations and delusions of infidelity on the part of her husband and, finally, had entered Manteno State Hospital from the county jail, where she had been detained as a vagrant. She had reversed with electroshock therapy over a period of six weeks, but relapsed within eight days of cessation of electroshock therapy. Her response to reserpine was rather dramatic in that the sensorium again cleared in the first week of reserpine therapy. She has made an excellent outpatient adjustment for over four months, and is once more running her home in a responsible fashion. An interesting sidelight of this patient's clinic progress is that the husband reports unusual warmth and affection, compared to the last ten years, and even plaintively asked the clinic physician on one visit if the dosage couldn't "please be cut about in half, doctor."

Since then, 10 more of this group of 22 have been discharged from the hospital, following a similar follow-up plan with the full cooperation of the Chicago Mental Health Center. Each patient and her relatives are given detailed instructions at the time of discharge. The usual maintenance dose is one mgm. per day, taken at bedtime. Clinic check-ups are made on pulse rate, blood pressure, and general well being every two or three weeks.

In addition, six more of these patients are in excellent contact, show few if any schizophrenic residuals, and are ready for some type of discharge from the hospital, but social planning is as yet incomplete. Unfavorable home conditions may make a family-care or domiciliary type of release necessary. Three others have shown definite improvement, either in cosmetic appearance, increased socialization, or a desire to be constructive on or off the ward in some industrial assignment. The remaining two can be considered unimproved. One of these two was discharged from the hospital in the care of an extremely unstable mother. She remained out only long enough to attempt to commit her mother and was forcibly returned. This traumatic experience, lasting about 48 hours, was sufficient to cause the patient to relapse severely.

In summary, then, 77 per cent of this group of 22 have either been successfully discharged or are ready for discharge; 8 per cent more are improved; and only 5 per cent show no change of any degree except that they no longer require maintenance electroconvulsive therapy.

Group II. On August 24, 1954, another group of 19 essentially similar "shock-reversible" chronic maintenance shock therapy female patients were placed on reserpine therapy using a slightly different treatment schedule. During their final week on electroshock therapy, oral dosage of reserpine was begun, varying from 2 to 3 mgm. per day, depending upon the weight of the patient. After one week of combined electroshock-reserpine therapy, electroshock was discontinued.

The usual side effects were noted, as in Group I, but to a lesser degree. The same type of response obtained with less noticeable effects on blood pressure and pulse rate. In addition, three of these patients had minor relapses at their expected relapse time. One required three electroshock treatments, another required two treatments, and the third required one. It was noticed that the threshold for convulsion in all three of these patients was markedly diminished; *i.e.*, less voltage and shorter duration of current was required to bring about the desired major convulsion.

No further relapses occurred and, at the time of this compilation, a total of nine patients have been discharged from the hospital; six more are awaiting social service planning and are deemed to have made a satisfactory social recovery; two are improved; and the remaining two are unimproved. The percentages, then, in this group are seen to be essentially similar to the first: 78 per cent either discharged or ready to leave the hospital, 11 per cent improved, and 11 per cent unimproved.

Group III. As these favorable responses began to appear, it was decided by the authors to abandon the chronic electroshock program and, on November 10, 1954, the remaining 41 "shock-reversible" female patients then on chronic shock treatment were started on reserpine. These patients were given combined oral and intramuscular reserpine in the following manner: each patient received 2 mgm. orally at bedtime. In addition, on alternate days for a one month period, each patient received from 2.5 to 5.0 mgm. intramuscularly for a a total of 15 injections.

At the end of the month, oral dosage was continued at 2 mgm. per day, then gradually decreased to 1 mgm. per day as responses stabilized. Although this group has been under study for only a little over two months, the following results have been obtained: 18, or 44 per cent of the patients, have been discharged from the hospital; 9 more, or 22 per cent, are awaiting discharge; 7, or 17 per cent, have shown steady and continuing improvement; and the remaining 7, or 17 per cent, have shown no appreciable change.

One of the patients discharged from this group presented a particularly difficult problem in that she and her entire family were faithful followers of a religion disdaining medical assistance. Although definite psychotic symptoms had appeared as early as the age of 18, the family had avoided commitment for five years, until 1937, when the patient had become so violent toward her relative and neighbors that court action was necessary. Various conditional discharges and releases against medical advice followed, with violent outbursts when out of the hospital, until April 1949, when the patient entered Manteno State Hospital on her current admission. By this time, she was mute and untidy, but subject to periodic rages. A course of 20 electroshock treatments was tried with no response, and the patient resided on progressively more deteriorated wards until 1953. At that time, her behavior was so destructive that maintenance electroshock was ordered. A total of 77 more treatments were given for control purposes and a definite eight-day relapse rate was observed. On reserpine therapy she rapidly cleared, was amazed to discover that it was December 1954, and stated, "If those tablets have done this for me, I am through with that religion." She has since been attending the clinic regularly, taking the medication daily despite her mother's protests, and is steadily employed.

Use of Reserpine in Shock-Resistant Patients

Various groups of severely regressed, very long-term (5 to 30 years of continuous hospitalization) were then surveyed to see whether this medication could be successfully administered in wholesale fashion to the typical "backward" patient with any expectation of improvement. These patients had all received, at various times, different types of intensive treatment from the earliest methods, through the eras of metrazol and large-scale insulin therapy, then electric shock, and had shown a uniform lack of response. In addition, many of them had been subject to other types of treatment such as carbon-dioxide therapy, prolonged-sleep therapy, and varied new medications as they would appear and then disappear from the market. More subtle techniques had been tried on occasion. Whole wards would be shifted, personnel would be changed, and whole teams of the ancillary therapists would make sustained efforts through the media of occupational and recreational therapy to bring about some change in the schizophrenic withdrawal of these untidy, severely regressed patients. All such measures were to no avail. For the purposes of this paper, these patients are referred to as "shock-resistant" and constitute the growing population of the hospital, for many enter at 16 to 18 years of age and remain 50 or 60 years.

Group IV. In a ward locally classified as "idle, untidy, irritable," housing 160 patients with various types of chronic deteriorating mental illnesses, 54 chronic schizophrenic women were selected because of their freedom from accompanying somatic disease. On Nov. 12, 1954, these patients were started on a treatment program identical with that of Group III. The results in appearance, eating habits, cosmetic interest, and reversal from incontinence to continence were remarkable and seem to be continuing as therapy progresses. After two months of treatment, 28 or 52 per cent are remarkably improved. Four of these patients have been discharged from the hospital, an event almost unprecedented from this type of ward. Three more are awaiting social service plans, having made apparent social recoveries to careful evaluation. Among those showing improvement should be mentioned one woman of 48, a former schoolteacher now institutionalized for the past 16 years, who has received, among other types of treatment, an especially large number of electroshock treatments over the years. She is now more affable, in good contact and, except for a continuous desire to go back to teaching school, could probably be released. The remaining 26, although showing no outward signs of notable improvement, are more quiet and amenable to direction. It has been noted that not one of these 54 has been involved in an injury, assault, or required hydrotherapy or sedation since therapy began. The 100-odd patients not so treated continued to be involved, at their usual rate, in the frequent injuries, assaults, escapes, and other disturbed episodes commonplace to any ward housing such severely regressed patients.

Group V. In another ward, 22 equally "shock-resistant" but not so outwardly regressed (*i.e.* clothed and tidy) female patients were started on the same treatment program as in Groups III and IV on Nov. 17, 1954.

After two months of therapy, 14 or 64 per cent were definitely improved. Of these, four were discharged from the hospital, four more are awaiting planning and ready for discharge, and six have shown varying degrees of the improvement mentioned before. One of these, a mute catatonic of three years' duration, suddenly began to talk, expressed a desire to be examined physically. It developed, during the interview, that she was very concerned over a "chest pregnancy" which she believed had resulted from an extramarital oral intercourse several years prior. This type of accessibility to deeply compartmentalized fears, anxieties, and guilt feelings has been demonstrated innumerable times when patients are on rather high dosages. Later on, as what we have come to call the "chemical barrier to anxiety" effect of the drug takes place, these feelings are either repressed again or perhaps disappear. The remaining eight, or 36 per cent, have shown no appreciable improvement as yet, but therapy continues, as it does with all the groups.

Group VI. A miscellaneous group of 10 patients having various psychoses accompanied by mild pulmonary tuberculosis had all required intermittent shock treatment for several years to control their extremely violent, destructive behavior, which was interfering with the tuberculosis therapy program.

Seven of these were chronic schizophrenics, and reserpine therapy was started on them on Nov. 10, 1954, according to the same treatment schedule used in the last three groups. After two months of therapy, two of these are ready for discharge as soon as their physical condition permits, three more are markedly improved and no longer require electroshock, and the remaining two are unchanged. The drug had little effect on the three nonschizophrenic patients: the first a severe mental defective, the second a patient with ablation of both frontal lobes, and the third a severely deteriorated epileptic.

Four other recently lobotomized female patients whose primary diagnosis was that of psychomotor epilepsy with chronic schizophrenic reactions of various subtypes were also given a course of reserpine therapy to see if any affective or other changes could be evoked. Three of these were considered to be mildly improved, in that they required less attention and expressed toilet urges; the fourth of that group was unchanged.

Group VII. A final group of 14 women and 35 men, many of whom had not only been subjected to all the various forms of standard intensive therapy, but who had also experienced a series of convulsions induced by some of the newer biochemicals still under research study, were placed on the combined oral-intramuscular reserpine therapy on Nov. 19, 1954. These patients ranged in age from 22 to 46 years with a minimum of 4½ years' continuous hospitalization up to a maximum of 16 years—the average being about 8 or 9 years. Most were untidy, irritable, and severely regressed.

After two months of combined oral and intramuscular reserpine therapy of these comparable groups, the greatest improvement was noted in the females. By and large, the men remained uninterested in personal appearance, and improvement was judged primarily on the basis of improved contact, reversal of untidiness, and increased affability.

Of the 14 women, 10, or 71 per cent, had improved, including one who, for the first time, could be considered ready for discharge. The remaining four showed little, if any, change. Of the 35 men, 14, or 40 per cent, had improved, including one who, after 13 years' continuous hospitalization, was deemed ready for discharge.

Addendum

Since the writing of this paper, the relatives of two patients have called the hospital, concerned over what appeared to be signs of approaching relapse. Both of these relapses were due to errors in maintenance dosage. In one, the prescription had been misread, so that the patient was receiving 0.1 mgm. tablets instead of 1.0 mgm. tablets. In the other, an unknown medicine, not reserpine, had been substituted. When these errors were corrected, the patients regained their former good state of contact.

Summary

(1) The results of treatment with reserpine on a total of 221 chronically-ill patients over a two- to six-month period are presented. These include 186 women, all but 7 of whom are chronic schizophrenic patients and 35 men, all severely regressed chronic schizophrenics.

(2) An effort was made to select a fairly representative cross-section series of groups of long-term patients, all of whom had received standard forms of therapy without response and had an extremely poor prognosis.

(3) The "shock-reversible" women, 82 in number, responded so dramatically that the chronic maintenance electroshock program was abandoned. Fifty-nine of these patients have been discharged from the hospital or are awaiting social planning, but are deemed ready for discharge. Only 11 are unimproved, the remainder showing varying degrees of improvement.

(4) The "shock-resistant" group, including 104 women and 35 men, have been under treatment for only two months. Of these, 19 are discharged or ready for discharge after hospitalizations up to 13 years. Fifty-two show definite clinical improvement. The remainder have not yet shown response to therapy.

(5) In view of these results, the authors believe reserpine to be a valuable new adjunctive or even replacement therapy in the treatment of chronic schizophrenic patients who were formerly considered more or less permanently institutionalized. We plan, at our hospital, to continue increasing investigation on a larger scale in both this problem and in the other types of mentally ill patients who constitute our population.

Acknowledgments

The authors express their indebtedness to Doctor Otto L. Bettag, Director, Department of Public Welfare, State of Illinois; Doctor Percival Bailey, Director, Illinois State Psychopathic Institute; and Doctor Richard J. Graff, Superintendent, Manteno State Hospital, for their advice, encouragement and support in this project, and to Mrs. Lorraine Bagby, R. N., Chief Nurse, Manteno State Hospital, and the members of her staff, particularly Mrs. Mary Hogan, Psychiatric Aide, for their continuous help in assisting with the treatment program and their invaluable detailed observations and reports.

THE CONTROL OF DEVIANT BEHAVIOR IN CHRONICALLY DISTURBED PSYCHOTIC PATIENTS BY THE ORAL ADMINISTRATION OF RESERPINE*

By Brian C. Campden-Main and Zygmunt Wegielski
Central State Hospital, Petersburg, Va.

Purpose of Study

This study was designed to assess objectively and, if possible, to measure the effectiveness of reserpine (Serpasil) in controlling deviant disturbed behavior in "backward patients" such as are found in all our state mental hospitals.

Experimental Design

Physical setup. Central State Hospital is situated in Virginia and has an inpatient population of approximately 4550. All of the patients are colored.

The entire study was conducted in the building that houses our most disturbed female patients. This building has a capacity of 188 patients and is divided into one ward on the first floor and one ward on the second floor. This group of patients was chosen because the ward population is relatively stable and the patients in the ward are, by and large, the most disturbed patients we have in the hospital.

Selection of patients. From this group of 188 patients were excluded: (1) any patient who had been hospitalized for less than three years; (2) any patient whose menstruation was irregular or in any other way deviant; (3) any patient who had been receiving any specific form of therapy, such as electroshock or psychotherapy, during the one month preceding the experiment; (4) any patient suffering from chronic brain damage; (5) any patient suffering from any physical or medical disability; (6) any patient who refused to take a placebo tablet by mouth for three consecutive days; and (7) any patient who was not chronically disturbed.

This exclusion left us with a "homogeneous" group of 41 patients who might well be described as "the worst behavior problems in the hospital."

These 41 patients were randomly divided into Group A, which received reserpine in tablet form, and Group B, which received placebo tablets, identical in all respects to the tablets received by Group A except that they did not contain reserpine.

TABLE 1 shows a breakdown of these two groups and demonstrates that they are fairly matched.

TABLE 2 shows the breakdown in diagnostic categories.

Dosage schedule. During the first two weeks of the experiment, hereinafter referred to as period No. 1, all patients swallowed one tablet each morning. During the second two weeks, period No. 2, each patient swallowed two tablets. A similar increase continued through periods Nos. 3, 4, and 5. Thereafter,

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* This paper is published with the approval of the Commissioner of Mental Hygiene and Hospitals for the Commonwealth of Virginia. The views expressed in this paper are those of the authors and do not necessarily reflect the opinion of the Department of Mental Hygiene and Hospitals.

TABLE 1

ATTRIBUTES OF GROUPS

	Group A (Serpasil) 21 patients			Group B (placebo) 20 patients		
	Mean	Standard deviation	Standard error of mean	Mean	Standard deviation	Standard error of mean
Age	41	10	2.2	40	8	1.8
Years in hospital	14	9	2.0	14	7	1.6
Blood pressure: systolic	144	20	4.5	145	25	5.7
diastolic	83	8	1.8	87	9	2.1
HAS score	15	14	3.1	14	12	3.0

TABLE 2

DIAGNOSTIC CLASSIFICATION

	Group A (Serpasil) 21 patients	Group B (placebo) 20 patients
I. Affective reactions		
Manic	8	6
II. Schizophrenic reactions		
Simple	2	1
Hebephrenic	2	5
Catatonic	5	1
Paranoid	2	6
Chronic undifferentiated	1	1
III. Other disorders	1	
Total	21	20

the dosage remained at five tablets each morning until the completion of the study.

Refusal of Medication

Because reserpine, when taken by mouth, has a cumulative, delayed action, there was no particular concern if a patient refused medication, provided that dosage was made up on subsequent days. The following schedule was used for this purpose:

Medication refused for 1 day—Double medication for next 1 day.
Medication refused for 2 days—Double medication for next 2 days.
Medication refused for 3 days—Double medication for next 3 days.
Medication refused for 4 days—Double medication for next 4 days.
Medication refused for 5 days—Patient dropped from study.

It is a credit to the patience of the nursing staff that no patient had to be dropped from the study because of refusal to take medication.

Evaluation

At the end of every two-week period, each patient was evaluated by the junior author and the nursing staff, using the Hospital Adjustment Scale (HAS) of Ferguson, McReynolds, and Ballachey.* The completed questionnaires were returned to the senior author, who scored each blank and kept the records. There was no communication between the senior author and the junior author, nor between the senior author and the ward personnel as to the ratings each patient had received from the HAS.

A brief progress note was also written on each patient by the junior author, assessing clinically the amount of improvement or otherwise at the end of each two-week period. The senior author did not see these notes until the completion of the study.

Finally, each patient's blood pressure was taken at the end of each two-week period.

The Hospital Adjustment Scale of Ferguson, McReynolds, and Ballachey "is a list of statements about behavior. These statements have been so selected as to be descriptive of the behavior of many psychiatric patients. Each of the statements may be marked as *true* or *not true* for a given patient, and when so marked the scale furnishes a fairly comprehensive summary of the patient's behavioral patterns. Each statement has been keyed in such a manner that it is possible to obtain a score indicative of the patient's general level of hospital adjustment."* The HAS scores are percentile scores and show directly where a given patient stands with respect to all the patients used by McReynolds and Ferguson in their normative sample.

Results

HAS ratings. The HAS score of each patient was determined at the end of each two weeks, as well as at the beginning of the experiment. The mean, standard deviation and standard error of the mean of the scores of the two groups were then determined. The progress of the two groups is represented graphically in FIGURE 1, which shows the mean percentile position of the patients in each group as compared with the normative sample used by McReynolds and Ferguson. The percentile rank of each patient in the experiment was also determined in relationship to the other patients in the experiment, and the mean, standard deviation and standard error of these percentile ranks was determined for each group for each period. This mean is also represented on FIGURE 1.

If reserpine is effective in improving deviant behavior, one would expect that the mean HAS score for the reserpine group would rise, while the mean HAS score of the control group would remain stationary. This result is demonstrated in the lower graph on FIGURE 1. One would also expect a rise in the mean percentile rank of the reserpine patients at the expense of the patients in the control group. This difference also is demonstrated in the graph on FIGURE 1.

Bearing in mind that optimal therapeutic efficiency is not achieved from oral reserpine for approximately two weeks and, further, that HAS ratings are based on a two-week observation period, it will be apparent that the percentile

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* Hospital Adjustment Scale for Evaluating Patient's Behavior in a Psychiatric Hospital, by E. L. Ballachey, J. T. Ferguson, and F. McReynolds. 1951.

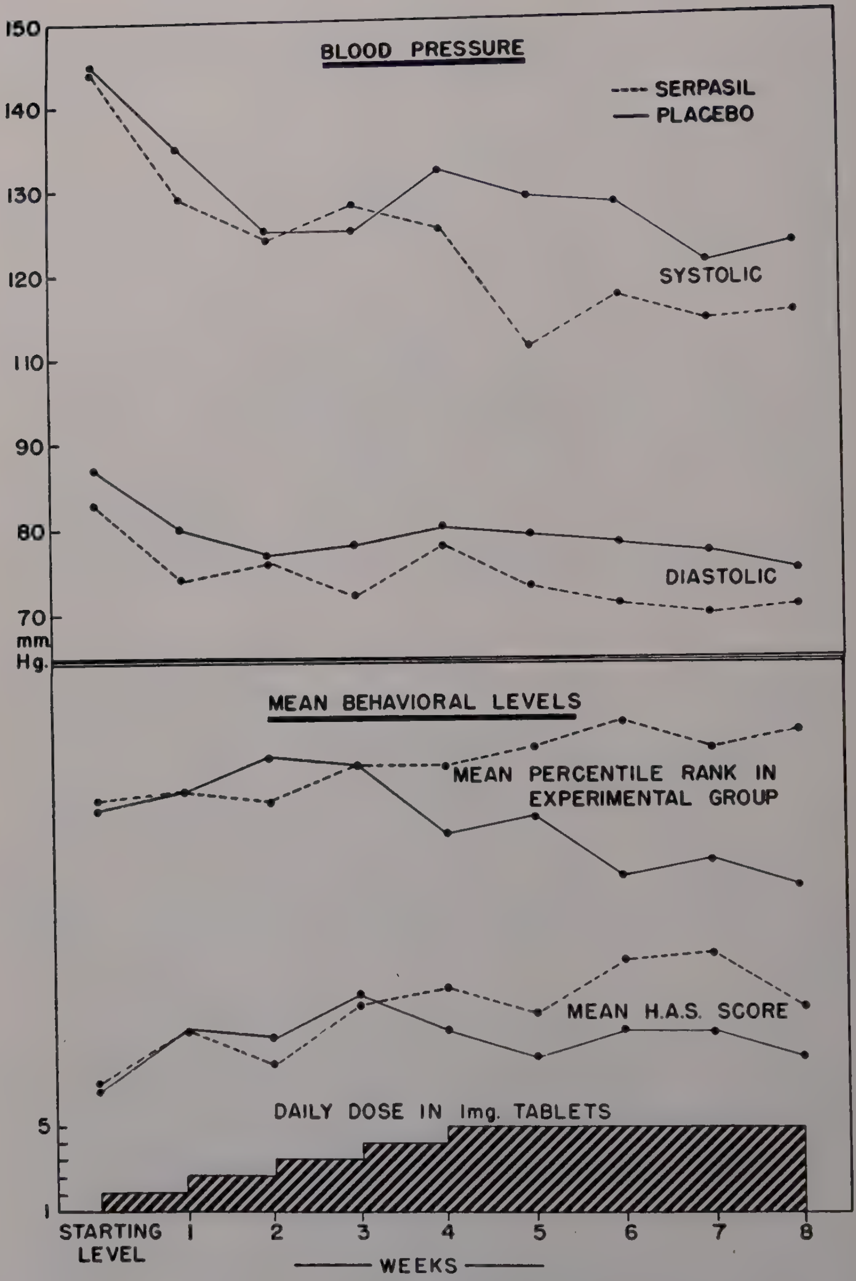
150
140
130
120
110
90
80
70
mm
Hg.
BLOOD PRESSURE
---- SERPASIL
—— PLACEBO
SYSTOLIC
DIASTOLIC
MEAN BEHAVIORAL LEVELS
MEAN PERCENTILE RANK IN EXPERIMENTAL GROUP
MEAN H.A.S. SCORE
DAILY DOSE IN 1mg. TABLETS
5
1
STARTING LEVEL
1
2
3
4
5
6
7
8
WEEKS

FIGURE 1

Table 3

Clinical Evaluation

Improvement rating	Group A (Serpasil) 21 patients	Group B (placebo) 20 patients
Unchanged	7	13
Slightly improved	8	5
Improved	4	1
Much improved	2	1
Percentage unchanged	33%	65%
Percentage showing some degree of improvement	67%	35%
Percentage according to degree of improvement		
Slightly improved (or better than)	67%	35%
Improved (or better than)	29%	10%
Much improved	9.5%	5%

rank at the end of, for example, period No. 6 will reflect the effectiveness of the reserpine given during period No. 5.

From the graphs, it becomes apparent that no reserpine effect appears until the end of experimental period No. 4, which corresponds to a dosage of 3 milligrams of reserpine a day, and that full effect is not obtained until period No. 6, when the reserpine dosage was at a level of 5 milligrams per day.

Clinical observations. As mentioned previously, each patient was assessed clinically by the junior author at the end of each period and, finally, at the end of the whole project. At this final rating, patients were categorized as:

Unchanged. No improvement in the patient's condition.

Slight improvement. Patient is quieter and more cooperative, less aggressive. Destructiveness and impulsivity reduced. No change in mental status.

Improved. Marked improvement in behavior generally, together with some improvement in mental status.

Much improved. Definite and marked improvement in behavior (for example, instead of being excited, unmanageable, and aggressive, patient is quiet, cooperative, and helpful). Mental condition also shows obvious improvement. Able to carry on relevant conversation. Conversation has lost much of its psychotic content.

This evaluation is tabulated in TABLE 3 for both groups. We note from this chart that two thirds of the patients in the reserpine group show some improvement, as compared with only one third of those in the placebo group; further, that three times as many patients in the reserpine group (nearly 30 per cent) were improved or much improved, as compared with only 10 per cent of those in the control group.

Discussion

It would not be correct to imply that the results obtained in our group of patients were disappointing. It should be stated, however, that there was little dramatic improvement in our patients, and our results are not as spectacular as those reported by several other investigators. In looking for a reason for this, several possibilities come to mind.

First, there is no doubt in the minds of the authors of this paper that the patients chosen for the project here reported were as refractory to any form of treatment as almost any patients could be. Nearly all of them were very "deteriorated"; and, as we have seen, they all belong in the group of chronic long-stay patients. For this reason, spectacular results with any form of drug therapy should not be expected.

Second, the dosage used by us was lower than that reported by many investigators. We are planning, at this time, a further study using higher dosage on this same total group of patients. It is our opinion that we did not get optimal effectiveness with even the 5-milligram dosage.

Finally, whereas most reserpine research has been done with white patients, all of our patients are Negroes. To hypothecate a differential racial response to this drug would not only be unwise but also unwarranted at this point in our research. This question, however, may be worthy of further investigation.

Conclusions

We may conclude from our observations that reserpine, when taken by mouth, is ineffective in controlling deviant behavior patterns in chronically disturbed female colored patients until a dosage of at least three milligrams per day is reached; and, further, that five milligrams per day is the minimal dosage if anything like optimal therapeusis is desired.

Acknowledgment

The authors wish to express their appreciation to Ciba Pharmaceutical, Products, Inc., Summit, N. J., for their many helpful comments and for supplies of Serpasil and placebo tablets.

CLINICAL EVALUATION OF RESERPINE IN A STATE HOSPITAL

By William L. Kirkpatrick and Foster Sanders
East Louisiana State Hospital, Jackson, La.

Purpose of Study

The purpose of this study was to determine the clinical effectiveness of reserpine (Serpasil)* on selected groups of psychiatric disorders at the East Louisiana State Hospital in Jackson, La. Our interest in initiating the study was stimulated by the recent favorable reports of the effectiveness of reserpine in other state hospitals and clinics (Raymond Harris, 1954; Nathan S. Kline, 1954). We had observed, in a few cases, the obvious quieting effect obtained by the oral use of the drug in small dosages, and we felt that, if more dramatic results could be achieved by larger doses and parenteral use, it would be an exceedingly valuable addition to the pharmacologic armamentarium of psychiatrists. A review of the available literature made at the time this study was contemplated failed to reveal any extensive reports on the use of reserpine in the treatment of epilepsy, extrapyramidal tract disorders, or tuberculous mental cases. Consequently, our study groups were chosen, in part, to cover these conditions as well as a variety of other mental disorders.

Our study totaled 206 patients consisting of 5 groups.† These groups were as follows: (1) 11 acutely disturbed patients; (2) 39 chronic epileptic patients; (3) 22 chronically ill patients residing in a violent ward; (4) 24 psychotic patients with pulmonary tuberculosis; and (5) a supplementary mixed group totaling 110, including (a) geriatric patients; (b) cases refractory to a large number of EST treatments; (c) deterioriated patients who were denudative, assaultive, destructive, and uncooperative; and (d) mental defective patients.

Experimental Procedure and Choice of Patients

Acutely disturbed patients. Eleven acutely disturbed patients were selected without regard to age, sex, diagnosis, or time in the hospital. There were 8 females and 3 males in the group with a variety of diagnoses, 9 of the 11 being of a schizophrenic nature. One had cerebral palsy and the other was diagnosed as chronic brain syndrome associated with convulsive disorder with psychotic reaction. The age range was 23 to 58 years, with an average age of 38. The average length of stay in the hospital was five and one-third years. These patients received initially five mgm. of reserpine intramuscularly (i.m.), and this dose was repeated as often as necessary if their blood pressure response was within safe limits, until their acutely agitated state was brought under control. As soon as cooperation was achieved with parenteral reserpine, the patients were started on an oral dose of one mgm. daily. If further parenteral medication was needed to control recurrent excitement, the oral dosage was concomitantly adjusted upward to a level not exceeding four mgm. daily. The immediate effectiveness or response of the drug was determined by the rapidity and extent of improvement of the agitation, the decrease in the need for restraints or electric shock therapy, and the initial change in the patient's behavior.

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* Reserpine (Serpasil) used for the major part of this study was kindly supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

† Three additional cases not included in the groups were treated and evaluated.

Chronic epileptics. The epileptic group chosen for study was an entire ward of 39 male patients who were receiving the usual antiepileptic medications in variable dosages. The three main medications in use were dilantin, mesantoin, and phenobarbital. These dosages were held constant for each patient during the entire experimental procedure. There was a large variety of diagnoses in this group, but the majority were suffering from *grand-mal* type seizures, due to a multiplicity of etiologies. The age range of the total chronic epileptic group was from 23 to 69 years with an average age of 44.1 years. The average length of hospital stay was 13.6 years. Age range in the experimental group was 22 to 69 years with an average age of 41.1 years. The control group age ranged from 35 to 66 years, the average age being 47 years. The average length of hospital stay in the experimental group was 10.5 years and, in the control group, 16.8 years. Range of hospital stay in the reserpine group was 4.2 to 28 years and, in the control group, 4.5 to 35.6 years. The patients were assigned to two groups matched with respect to seizure frequency over the previous five months. The experimental group received 1 mgm. of reserpine daily for a period of 45 days, and the control group received a placebo. In both groups, the existing antiepileptic regime was continued, and other factors were maintained as constant as possible. Results were evaluated by comparing the mean seizure frequencies of both groups for the last 30 days of a 45 day period of treatment against their monthly average seizure frequency for the previous 5 months, and comparing the seizure frequency of the control group to that of the experimental group during the last 30-day period of medication. A 15-day period was allowed for any possible cumulative effect.

Chronic patients residing in a violent ward. Twenty-two males, chronically ill residents of a violent ward, were included in this group. There was no selection according to age, diagnosis, or duration of illness. Approximately 50 per cent were chronic schizophrenic patients. The remainder were a mixture of epileptics, manics, and paretics. Their ages ranged from 18 to 64 years with an average age of 38.3 years. Their average length of hospital stay was 3.5 years and the range of hospital stay was 1 month to 11.3 years. They were given 1 to 4 mgm. orally daily for a period of 45 days. Dosage increased by 1 mgm. daily each week for four weeks, or until a definite effect was noted or toxic effects observed. Their previous behavior pattern was compared with their behavior during the treatment period for any significant change.

Tuberculous group. Twenty-four psychotic male patients with pulmonary tuberculosis were included in this group. Age range was 15 to 64 years, the average age being 44.1 years. The average length of hospital stay was 13.4 years. The length of hospital stay ranged from 7 months to 34.9 years. Some of these patients were in restraint and were suffering from a rapid progression of their pulmonary disease, due in part to their refusal to take their medication or to cooperate with other phases of their treatment. Parenteral plus oral medication was used in 14 patients and oral alone in the other 10. In the oral group, dosage was maintained constant at 2 mgm. daily. Intramuscular reserpine was administered to 14 tuberculous patients in dosages of either 5 or 2.5 mgm. i.m., 5 mgm. being injected initially. Oral dosages of 2 mgm. a day were initiated, to be adjusted upward if necessary. The frequency and amount of injections were determined in a manner similar to that of the acutely disturbed group, that is, by the patient's blood-pressure response to the initial injection and his subsequent behavior. In this group, however, if his blood pressure response was considered within safe limits, he was given 5 mgm. i.m. every other day for a week and maintained on 2 to 4 mgm. a day orally. If the patient's behavior indicated a further need for parenteral injections but the blood pressure response had not been within safe limits, 2.5 mgm. was administered.

Supplementary mixed group. The supplementary mixed group was set up and studied for a period of two months following the completion of the observation of the other four groups. It included 110 patients consisting of geriatric cases, patients refractory to a large number of electric shock treatments, and a group of the most deteriorated patients in the hospital. The average age for the patients was 43.6 years, and the average duration in hospital was 7.8 years.

Ten male and female patients were chosen from the geriatric wards without regard to diagnosis or duration of illness. They were the loudest patients in the wards, and the most difficult to handle. Some were chronic complainers. Others were in restless and agitated states, or were in restraint and had to be bathed, fed, and dressed.

Fifty-five shock-resistant patients, 38 females and 17 males, were selected from chronic wards. The number of their previous shock treatments ranged from 1 to 319, 27 females and 12 males having received over 50 EST treatments. Of these 39, 12 had received over 100 EST treatments with no sustained response. Selection was made without regard to age, diagnosis, or duration of illness.

The remaining 35 were chosen from the back wards and were the most deteriorated, violent, assaultive, and unmanageable patients in the hospital. There were ten mental defectives in this group. All patients who would not cooperate with the oral administration of reserpine were started on i.m. reserpine. Oral reserpine was started as soon as possible. The parenteral injections were repeated as necessary to aid in the continuation of treatment and maintenance of the oral dosage. In those cases in which parenteral plus oral therapy was ineffective, electric shock therapy was added to the therapeutic regime. Eighty-five patients were given medication, and a group of 25 patients were randomly selected as controls.

Therapy in this experimental group consisted of oral reserpine, oral plus parenteral reserpine, or both, in combination with EST treatments.

Data Obtained on Patients

The data obtained on patients included: (1) blood pressure, temperature, and pulse rate weekly; (2) weights bimonthly; (3) pretreatment and periodic psychiatric evaluations by selected members of the hospital staff and authors; and (4) rating by the attendants and supervisors independently, on a weekly basis, using the Sol-Levy modification of the revised Malamud Sands rating scale.

Patients in all but the epileptic group were rated according to their response to therapy, using the above data by the following index: (1) marked improvement, including those patients who had a partial or complete remission of their psychotic process and/or a marked relief of signs and symptoms; (2) moderate improvement, including those who became more coherent and relevant, more cooperative, and showed a significant decrease in their apprehension and excitability, frequently retaining their delusions or hallucinations or symptoms, but showing less reaction to them; (3) slight improvement, merely indicating those patients who were easier to manage or who were more tranquil, occasionally expressing psychotic ideations or hostility and having inappropriate affect, but easier to manage; and (4) no change.

The epileptic group was rated in their response to therapy by the change in their seizure frequency as compared with their previous records before treatment. This group was not rated according to its total psychiatric response.

Results

TABLE 1 tabulates the results obtained with the acutely disturbed patients. Most of the patients, however, responded to some degree to the first injection. In one case, three injections of five mgm. were necessary to bring about an initial response. In some cases, it was necessary to give subsequent injections due to a recurrence of their excited state. One injection usually sufficed to return the patient to his controlled state. All the patients in this group became quieter and were easier to manage, and this was the only effect noted in

TABLE 1

RESPONSE OF 11 ACUTELY DISTURBED PATIENTS TO COMBINED PARENTERAL AND ORAL RESERPINE

(Individualized Dosage)

Name	Sex	Diagnosis	Total of 5 mg. injections	No. of injections before response	Response
V. P.	F	SR-P	1	1	Moderate
D. C.	F	SR-C	1	1	Moderate
W. S.	F	SR-C	2	2	Quieting
M. A. G.	F	C.P.	4	1	Marked
M. B.	F	SR-H	2	1	Moderate
M. C.	F	SR-Ch. Und.	1	1	Moderate
M. L.	F	SR-C	1	1	Quieting
G. S.	F	SR-C	3	3	Marked
A. D. Y.	M	Psy. Ep.	6	1	Marked
I. D.	M	SR-P	6	1	Quieting
A. D.	M	SR-Ac. Und.	3	1	Moderate

SR—Schizophrenic reaction
P—Paranoid
C—Catatonic
H—Hebephrenic
Psy. Ep.—Epilepsy with psychosis
Ch. Und.—Chronic undifferentiated
Ac. Und.—Acute undifferentiated
C.P.—Cerebral palsy

three cases. Five were moderately improved and were not only quieted, but became more coherent and relevant within a short time after administration of the drug. Three patients out of the group were markedly improved. It was noted in some patients, in this and the tuberculous and supplementary groups, that best results were obtained when parenteral reserpine was used to initiate therapy. A marked variability in the individual's response to both oral and parenteral reserpine was noted. This variability was reflected in the different dosages of the drug necessary to bring a patient under control, in the blood pressure response, and in the flushing effect. A differentiation is made between initial and over-all response, as shown in TABLE 1. In two instances, an injection of five mgm. had no apparent immediate effect, whereas subsequent doses produced marked changes. There appeared to be some correlation between the initial effect on blood pressure to parenteral reserpine, and the behavioral response with the most marked improvement was shown in those patients with the largest initial drop in blood pressure. Further investigation is indicated to verify this result. No patient in this group experienced a fall in blood pressure as a result of parenteral reserpine to a degree requiring supportative therapy. The necessary material, however—adrenalin, ephedrine, or wyamine sulfate—was available to combat such an event. Included below are two case reports in which there was a marked response.

Case Report on A. D. Y.

This patient was a 37-year-old colored male who had been affected by epileptiform seizures with loss of consciousness since the age of 13. His record revealed that he had congenital syphilis, and he had been diagnosed as having a chronic brain syndrome associated with convulsive disorders with psychotic episodes. There were numerous references in his record to homicidal, assaultive and violent behavior, and he was kept in constant restraint at all times. He had shown no sustained improvement in response to any form of therapy, including electroshock therapy, sedation, antiepileptic, and psychotherapy. He was felt to be an ideal candidate for parenteral reserpine, and was given 30 mgm. parenterally over a period of nine days and maintained on 2 mgm. a day orally. He became quiet and cooperative within the first few days, and restraints were removed. Within two weeks he was permitted ground privileges. Since the original parenteral injections, he has been maintained on oral medication effectively. It is interesting to note that, while on the medication, he has had no seizures, whereas they were occurring regularly several times monthly prior to reserpine therapy.

Case Report on M. A. G.

This patient is a 31-year-old white female with congenital spastic paralysis associated with a protracted labor and convulsions during her first nine months of life. Neurologically, she presented exaggerated tendon reflexes, extensive plantar responses, and choreoathetotic movements most marked in hands and face. There was associated dysarthria, and a difficulty in controlling the flow of saliva. Her psychological evaluation as measured by Weschler-Bellevue and Rorschach showed her to be of average intelligence and in good contact with reality. She had been in and out of the hospital on numerous occasions because of emotional problems resulting from her neurological condition. On her present admission, her behavior was characterized by depression, restlessness, tension, instability, and impulsive behavior. She was given parenteral reserpine in five mgm. doses daily for four consecutive days in conjunction with 2 mgm. a day orally. Following the initial injections, there was a marked reduction in her tremor and, subsequently, a marked improvement in her mental state. She lost her tenseness and anxiety, and her previous depression decreased. She was overwhelmed by the fact that she was able to hold a glass of water and drink for the first time without spilling the contents. Electroencephalograms had previously been attempted on this patient on several occasions, but were noninterpretable because of her severe involuntary movements. At the suggestion of Doctor Richard Paddison, Associate Professor of Neurology at the Louisiana State University Medical School, she was given five mgm. of parenteral reserpine 30 minutes prior to another electroencephalogram (EEG). This resulted in a perfectly legible electroencephalographic tracing with practically no muscle artifact (FIGURES 1 and 2). The EEG effect lasted from 26 minutes after injection to 1 hour and 10 minutes later. It is felt, in view of this result, that further research is indicated regarding the possible use of reserpine as an aid to the electroencephalographer.

Chronic Epileptic Group

The results for this group are represented in TABLE 2. In the experimental group of 19 patients, 11 decreased in number of seizures weekly, 4 increased, and 4 remained constant. In the control group, 7 patients showed an increase in number of seizures, 7 a decrease, and 6 remained constant. An analysis of the results revealed a statistically significant effect of the drug in decreasing the number of seizures and indicated that reserpine may be useful as an adjunct in the treatment of epilepsy. It was our further observation that intramuscular reserpine was effective in the immediate treatment of three cases of status epilepticus and apparently caused a cessation of the continuous seizures. It should be noted, further, that several epileptic patients treated in the other study groups showed a definite decrease in the number of their epileptic seizures while receiving reserpine. Most of these patients received larger dosages than the studied epileptic group, and the decrease in seizure frequency was most marked in those who received parenteral reserpine. Although the treatment results with the chronic epileptic group were not particularly dramatic, it must be remembered that these results were obtained in addition to the maximum effect which had been obtained with the usual anticonvulsive drugs and with a low dosage of reserpine.

Chronic Patients Residing in Violent Ward

TABLE 3 summarizes the responses of this group to oral reserpine. The results clearly indicate that reserpine is a good tranquilizing agent for such patients with few untoward reactions noted. The majority of the patients who were communicative stated that they felt better, slept better, and were

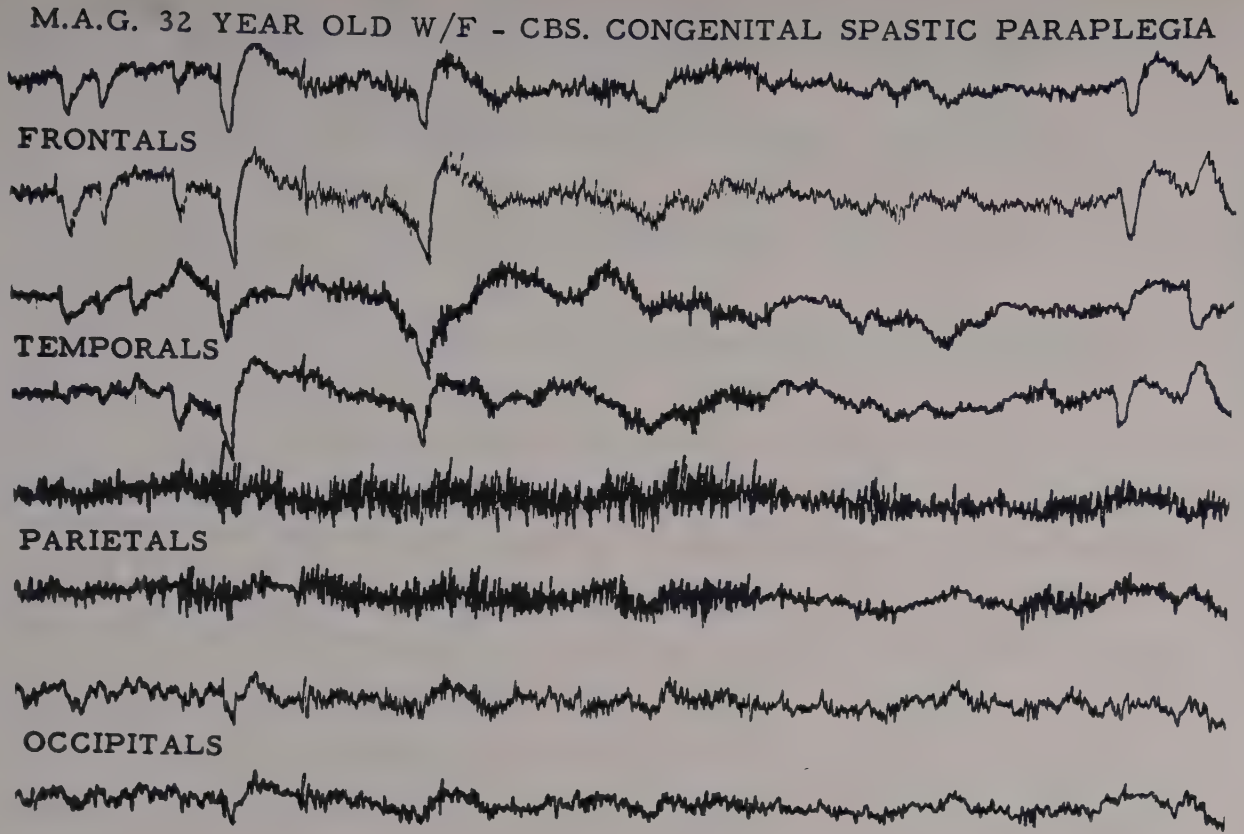

Figure 1. Before reserpine.

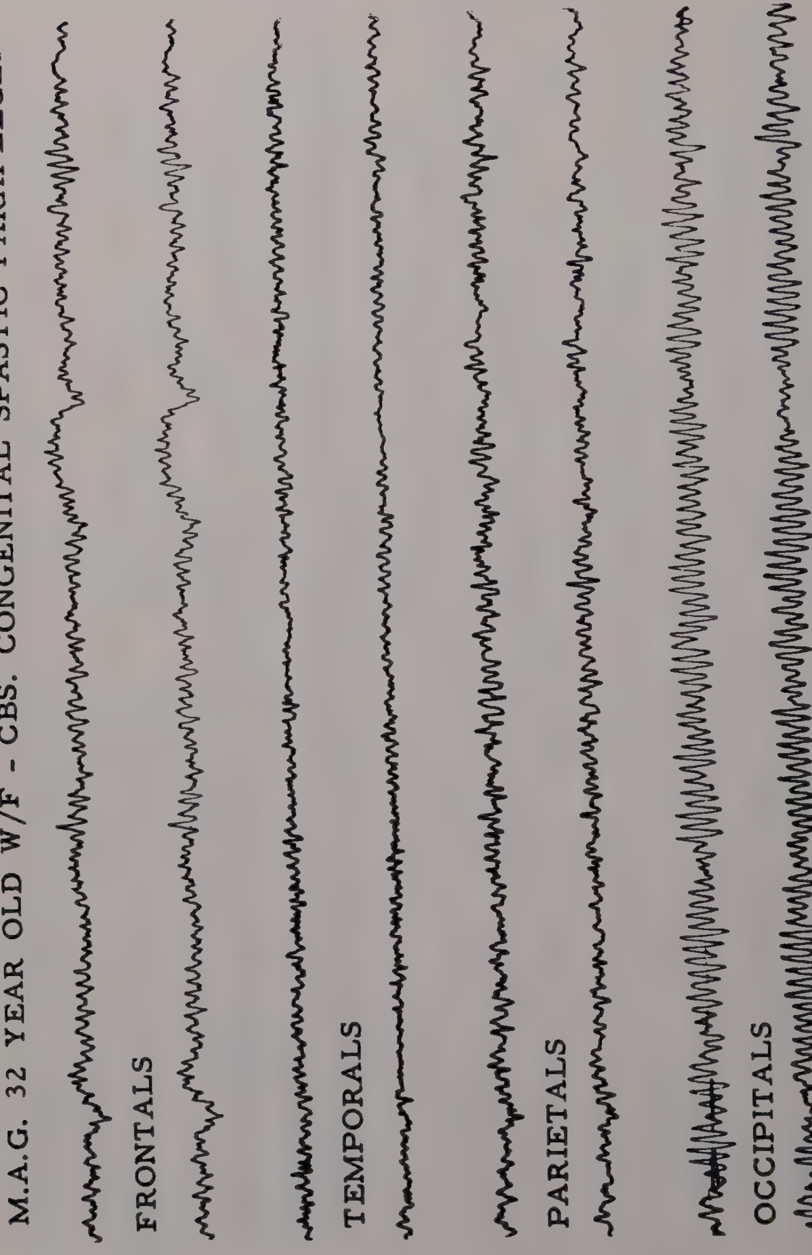

FIGURE 2. Fifty-four minutes after injection of reserpine, 5 mgm., i.m.

TABLE 2

THIRTY-NINE EPILEPTIC PATIENTS

Average of	Control (20 patients)		Experimental (19 patients) (1 mg. daily orally for 45 days)	
	Before placebo	After placebo	Before reserpine	After reserpine
Seizure frequency	2.5	2.3	2.8	2.0
Blood pressure:				
Systolic	130	120	131	108
Diastolic	84	76	85	72
Arterial pressure	107	98	108	90
Pulse	84	77	87	71
Weight	170	169	162	166

TABLE 3

TWENTY-TWO CHRONIC VIOLENT WARD PATIENTS

Results for 45-Day Period of 1 to 4 mgm. Oral dosage daily

Improvement

Marked*	5
Moderate	5
Quieting	12
No Change	0

* Three patients in this group received oral reserpine in conjunction with EST, neither of which had proven beneficial by itself.

less nervous. Three patients listed in TABLE 3 with marked improvement, and two with moderate improvement did not respond to oral reserpine alone, nor had they responded to previous EST treatments. When the two were combined, a sustained response was achieved.

Five patients in the group were discharged and seven were transferred to better wards. The remainder were improved to such an extent that they were easier to manage with a reduction in the number of necessary restraints and sedation. TABLE 4 gives the relationship of response to oral reserpine to diagnosis in this group. It is interesting to note that our results in this group by oral medication alone were better than those in our tuberculous patients that received oral reserpine alone. This response, in part, may be attributed to the higher dosage level given to the patients in this group or to the debilitating effect of the somatic disease associated with the mental illness.

Psychotic Tuberculous Group

Electroschock therapy was contraindicated in all of the active tuberculous cases in this series. It was noted that, even with relatively large drops in systolic and diastolic pressure, parenteral injections could be repeated safely, due to the fact that the largest drop usually occurred, initially, within the first four hours, dropping to a maximum but stopping within relatively safe limits. Prior to the administration of the drug, all of the patients treated were assaultive and unpredictable, and many were in restraints because of their

TABLE 4

RELATIONSHIP OF RESPONSE TO ORAL RESERPINE TO DIAGNOSIS IN 22 CHRONIC PATIENTS

Marked response:		*Slight Improvement:*	
Schizophrenic-catatonic	2	Schizophrenic-paranoid	1
Schizophrenic-paranoid	1	Schizophrenic-chr. undiff.	1
Manic depressive manic	2	Schizophrenic-catatonic	1
Moderate response:		Mental deficiency	1
Schizophrenic-catatonic	1	Undiagnosed	2
Schizophrenic-acute undiff.	1	Chronic brain syndrome associated with cerebral arteriosclerosis	1
Schizophrenic-childhood	1	Chronic brain syndrome associated convulsive disorder	4
Manic depressive manic	1	Central nervous system syphilis	1
Psychosis associated with Parkinsonism	1		

hyperactivity, destructiveness, and agitation. Most of this group refused any type of medication, were generally uncooperative, and hard to manage. Without exception, following parenteral reserpine, all 14 patients became more cooperative, quieter, and rested more frequently, taking their medications readily. In most cases, their appetite improved, and none of these patients required further restraint. They were all more cheerful and alert and easier to manage. A summary of their blood pressure changes, plus those of the patients in the acutely disturbed group, are shown in FIGURE 3. The other 10 psychotic tubercular patients were given 2 mgm. a day orally. The benefit they received at this dosage level was more slowly achieved and not as marked as when therapy was initiated with parenteral medication. A comparison of the increased effectiveness of parenteral and oral reserpine over oral alone is shown in TABLE 5. The relationship of response to diagnosis is given in TABLE 6. No correlation between diagnosis and response was noted. It is not known whether the difference in the parenteral group was due to the route of administration. A comparison of chest plates before and after six weeks of extensive reserpine administration revealed a marked improvement in several cases in the parenteral plus oral group, and no progression of the disease in the remainder. The observation period has been too short to determine the permanent effect, if any, that reserpine might have on the tuberculous process directly. It is obvious, however, that having calmer, quieter patients who eat better and cooperate in taking their antituberculous medication is a vast improvement over the opposite situation. Our small series point to a need for further study in this area and suggest the possibility that reserpine may become a valuable adjunct in the treatment of tuberculous mental cases. An abstracted case record of one of the patients (J. P.) who exhibited marked improvement is included, as follows:

Case Report on J. P.

This patient was a 32-year-old white male, classified as a mental defective, imbecile, low grade. He was a tuberculous patient with far advanced progression of the disease bilaterally. When first seen, he was markedly disturbed, assaultive, and had to be kept in constant restraint. His tuberculosis was aggravated by his constant hyperactivity, failure to eat, and refusal to take,

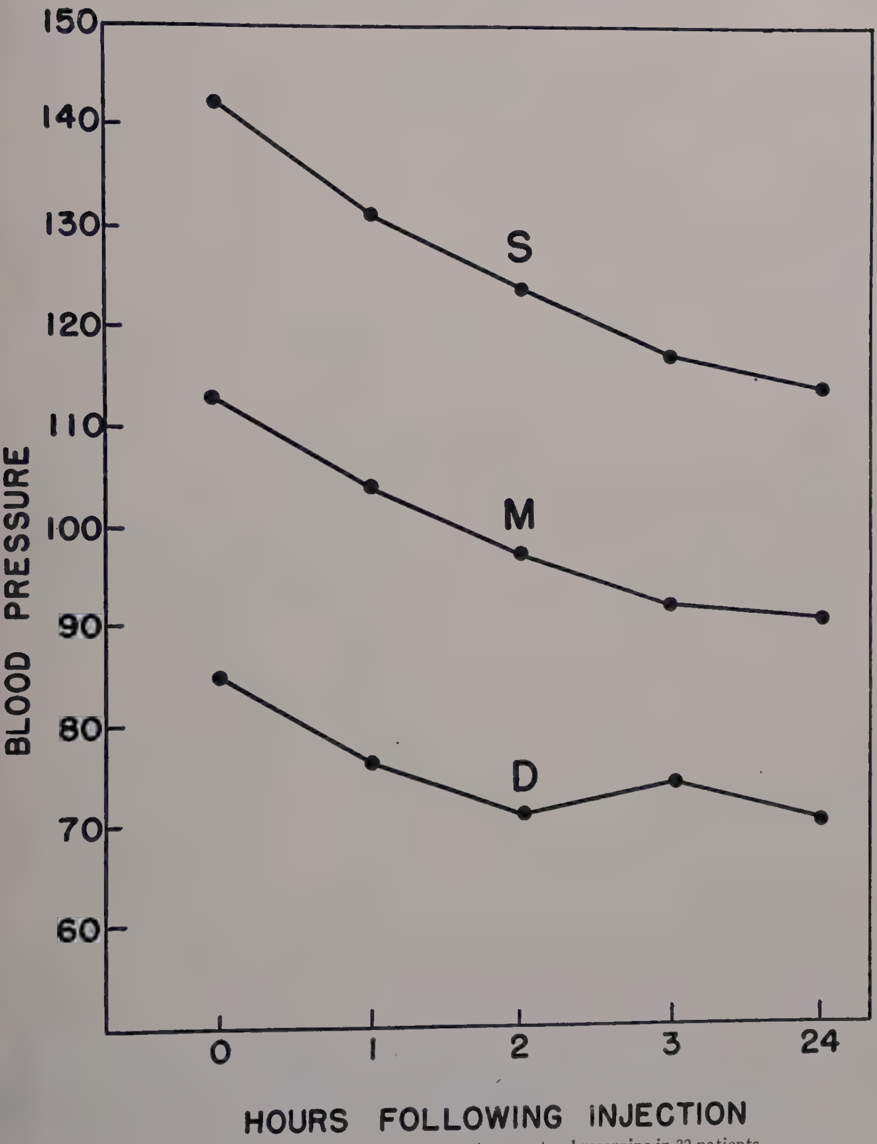

FIGURE 3. Initial blood pressure responses to parenteral reserpine in 22 patients.

or be administered, his antituberculous medications. He was given five mgm. of reserpine i.m., at which time the controlled blood pressure reading was 132/68. One hour later, the blood pressure dropped to 118/46 and, two hours following the injection, he flushed and remained so for approximately 45 minutes. Three hours after the injection, his blood pressure had stabilized around 114/118 over 50 to 60. Twenty-four hours later it was 120/60. He

TABLE 5

TWENTY-FOUR PSYCHOTIC TUBERCULOUS PATIENTS
A Comparison of Effectiveness of Parenteral and Oral Reserpine

Improvement	Combined parenteral and oral; 14 patients, individualized dosage	Oral alone; 10 patients, 2 mg. daily
Marked	3	0
Moderate	4	0
Quieting	5	6
No change	2	4

TABLE 6

RELATIONSHIP OF RESPONSE TO PARENTERAL AND ORAL RESERPINE TO DIAGNOSIS IN 24 PSYCHOTIC TUBERCULAR PATIENTS

Parenteral plus Oral			
Marked response:		*Slight improvement:*	
Mental deficiency, without psychosis	1	Mental deficiency with psychosis	1
Schizophrenic-paranoid	1	Psychopathic personality with psychosis	1
Psychosis unclassified	1	Schizophrenic paranoid	1
Moderate response:		Chronic brain syndrome associated with T.B. with psychotic reaction	1
Psychosis with psychopathic personality	1	Schizophrenic-catatonic	1
Simple adult maladjustment	1	*No change:*	
Schizophrenic-catatonic	2	Schizophrenic-hebephrenic	1
		Imbecile with psychosis	1

Oral Alone	
Slight improvement:	
Schizophrenic-paranoid	2
Mental deficiency	1
Schizophrenic-catatonic	1
Dementia praecox	1
Addiction alcoholism	1
No Change:	
Schizophrenic-paranoid	2
Chronic brain syndrome associated with convulsive disorder with psychosis	1
Mental deficiency, idiot	1

became very quiet approximately two hours after the injection and even attempted to help with the blood pressure determinations. The following day, the patient began taking 2 mgm. reserpine a day orally, and was given 2.5 mgm. reserpine i.m. with a maximum drop in blood pressure from 120/60 to 116/54 in 1.5 hours. He remained quiet and cooperative until the third day following the initial injection, at which time he became violent and attacked the attendants, remaining violent for five hours, when another 5 mgm. of reserpine was administered i.m. At the time of administration, his blood pressure was 98/48. An hour later, it was 110/50 and, two hours later, it was 100/44, where it stabilized. Forty minutes following the injection, he became quiet, cooperative, and cheerful. He continued to receive 2 mgm. of reserpine daily during

TABLE 7

RESPONSES TO RESERPINE IN SUPPLEMENTARY MIXED GROUP
(110 Patients)

Patient in group	Therapeutic method	Percentage improvement				
		Marked	Moderate	Slight	None	Total
47	Oral	17	28	23	32	68
10	Oral + shock	50	10	20	20	80
20	Parenteral + oral	25	20	35	20	80
8	Parenteral + oral + shock	0	37.5	37.5	25	75
25	Placebo	0	0	8	92	8

Improvement with reserpine by any therapeutic method—85 patients, 73%.
Improvement with pacebo—25 patients, 8%.

the study period. In six days, he received 20 mgm. parenterally and 2 mgm. a day orally. After the sixth day, i.m. reserpine was stopped and the patient continued to improve and remained cooperative. He took all medications and injections for his tuberculosis readily, in marked contrast to his previous attitude. He ate double helpings every meal and rested well. Ten days following the last injection, he was still described by attendants who had previously attended him for long periods as maintaining his improvement and as remarkably changed.

Supplementary Mixed Group

The responses of this group are represented in TABLE 7, expressed in percentage of improvement as related to the therapeutic method. In the oral-shock group, 50 per cent had marked improvement, as compared with 25 per cent marked improvement in the parenteral plus oral group. Both groups, oral plus shock and parenteral plus oral, had a total improvement of 80 per cent of their patients. Oral, alone, had only 17 per cent marked improvement, but a total response of 68 per cent improvement. There were no marked improvements in parenteral plus oral plus shock. The parenteral plus oral plus shock, however, represented the most deteriorated and unmanageable patients in the entire group and, despite no marked improvement, their total over-all improvement was 75 per cent, which was an excellent response for the group as a whole. Thirty-three out of 62 patients who improved in group five had an average number of 89 previous electroshock treatments. Out of 18 marked improvements in group five, 14 patients had received an average of 86 previous electroshock treatments.

Ten mental defectives were treated with reserpine with 50 per cent improvement, three being moderately, and two slightly improved. In the control group of five mental defectives, one improved slightly.

Fifteen patients 60 years or older were treated with reserpine and eight improved to some degree. In the control group of 10 patients 60 years or older, there was no improvement.

Out of 18 marked improvements in group 5, 13 were schizophrenic reactions and two affective disorders, the other 3 being a cerebral arteriosclerosis, a chronic brain syndrome with brain trauma, and a psychoneurosis.

In the group of 62 patients showing any type of improvement, there was an average weight gain of 5.6 pounds.

Dosage level in the oral group ranged from 1 to 7 mgm. daily, the majority receiving 5 to 6 mgm. daily before optimum effect was noted. Thirty-two per cent in the oral group showed no change in their psychiatric status even at this dosage level.

There were no appreciable toxic effects in the entire group. Two patients receiving parenteral therapy, however, had blood pressure drops down to 80/54 and 79/40, and were given ephedrine and wyamine with a gradual rise in blood pressure. They did not appear to be in shock or in acute distress. Sixteen out of the 28 patients receiving parenteral injections in this group had blood pressure drops down to the range of 100–80/70–50 associated with the injections. They had no significant complaints associated with the blood pressure change (oral).

Ninety-eight out of 110 patients in this group gained in weight. The greatest average weight gain occurred in the oral group of 47 patients, the average gain being 6.3 pounds. Total over-all improvement in this group was 67 per cent.

A complete statistical analysis of all data with correlation of response to age, diagnosis, duration of illness, blood pressure, weight gain, therapeutic method, dosage level, *etc.*, has not been completed at this time, but will be published subsequently.

Included below are seven case reports of patients in the supplementary mixed group who showed marked improvement. They represent patients who were treated by the three different therapeutic methods, oral alone, oral plus shock, and parenteral plus oral.

Case Abstract of P. M. (*Shock Plus Oral*)

Patient is a 52-year-old single white female who was first admitted to this hospital at the age of 16 years. History revealed a total hospitalization period of 35.8 years with a continued diagnosis of schizophrenic reaction, catatonic type. At the time of admission in 1918, she was denudative and acutely disturbed with a marked push of speech. She had also had periods of apathy, muteness, and negativism. Family history revealed two sisters and a mother who were mentally ill. She was raised in a home for foundlings and in the House of Good Shepherd, and had never had a normal family relationship. There was a history of seizures as a child. She completed only three years of school, and was a poor student. She had a rather stormy hospitalization here, with intermittent episodes of resistiveness, combativeness, and untidiness, mixed with periods of depression. One hundred and twenty-nine electroshock treatments were given her with no sustained improvement.

She was finally started on reserpine, one mgm. daily, and four electroshock treatments were given in conjunction with the medication. She showed remarkable improvement in response to this combination, was allowed out of restraint, became interested in her personal habits, helped in the ward, and has been granted yard privileges to run errands. She gained a total of 15 pounds in weight. She was subsequently permitted to leave the hospital on a pass, preparatory to convalescent leave.

Case Abstract on J. H. (Shock Plus Oral)

Patient is a 29-year-old white male Catholic welder who is married and has two children. History reveals a total of nine months' hospitalization in mental institutions. Complaints on admission here were overactivity, obsessive cleanliness, insomnia, hypochrondriasis, and irrelevance. Background revealed that he was the youngest of 12 children and had an essentially happy family relationship. He was indulged by his mother and older sister, however and apparently had life-long feelings of inadequacy and inferiority. He was a good-looking youth, a good athlete, and an average scholar. There was no previous history of mental illness and family history was negative for mental illness. He was diagnosed as having a schizo-affective disorder and was given four courses of electric shock therapy totaling 82 treatments. He showed improvement after two courses, to the extent that he was released on convalescent status. He relapsed each time, however, and within two or three weeks was returned to the hospital.

He was started on reserpine orally, one mgm. daily, and dosage was subsequently adjusted to two mgm. daily, combined with one electric shock treatment weekly for several weeks. He improved rapidly with this combined therapy and was released in complete remission, after six weeks on discharge, his condition being superior to that on his previous convalescent releases.

Case Abstract on J. M. (Oral)

Patient is a 54-year-old white male painter. He is Baptist in religion and is married. He had his first mental hospitalization in 1935, following a very serious brain injury for which he was treated by trephining and the aspiration of a subdural hematoma. Shortly after this operation, he manifested a marked personality change from an easy-going friendly person into an irritable, violent, explosive individual. He was first admitted here in 1939, at which time post-traumatic epilepsy was his diagnosis. He was discharged a short time later, but was in and out of the Veterans Administration and General Hospital almost constantly until he was readmitted in 1953. Readmission was necessary due to his inability to adjust on the outside and his potential dangerousness. Background revealed that he had five other siblings and had had an essentially normal birth and early development. He attended three years of high school and made a good adjustment. Following his head injury, he drank alcohol excessively. He developed weakness of the left side of his body and started having from three to six seizures monthly shortly after his injury in 1935.

He was started on reserpine oral medication in November 1954, at which time the dosage was adjusted upward to three mgm. daily. His seizures stopped, he became pleasant and affable, and lost most of his irritability. Speech became more coherent and relevant, and he is now being allowed maximum hospital privileges.

Case Abstract on Mrs. J. P. (Oral)

Patient is a 34-year-old white housewife, Catholic, who has spent a total of 37 months in mental hospitals, receiving, during this period, 210 electroshock treatments. Original diagnosis was manic depressive, depressed type. Complaints, on admission in 1947, were severe depression, auditory and visual hallucinations, delusions of persecution, and the idea that she was going to marry the devil. Background revealed a fifth-grade education, but difficulty in learning. She was one of nine siblings, with a congenial family relationship. She contracted an unhappy marriage in 1941, in which her husband refused to support her. She had two children by this union. Recently her diagnosis was changed to schizophrenic reaction, chronic undifferentiated type, due to continued evidence of deterioration, and no sustained response to therapy of any type.

She was started on oral reserpine, one mgm. daily, and the dosage was adjusted upward to five mgm. daily, at which level she obtained her maximum response. She is now cheerful and friendly, mixes with the other patients, and has gained in weight. She has again become interested in her appearance, recently asking for a permanent wave, whereas prior to therapy she had been sloppy and disheveled. She also attends recreational and social events. She was subsequently allowed to leave the hospital on a pass, preparatory to convalescent leave.

Case Abstract on W. S. (Parenteral Plus Oral)

Patient is a 37-year-old Baptist housewife who has spent 87 months in mental hospitals. She was admitted at the age of 29, being a transfer from DePaul Sanitarium, New Orleans, La., with a diagnosis of schizophrenic reaction, catatonic type. Information on admission here, in April 1946, revealed a history that included repeated attempts at suicide, even to the extent of biting her tongue and lips in trying to bleed to death. It was finally necessary to extract some teeth to prevent this procedure. She had a total of 183 shock treatments during her 87 months in the hospital, including 21 at DePaul. Background revealed that she was raised by her aunt, who had mistreated and abused her. She was a college graduate and was employed as a teacher. She had two children by her marriage and was devoted to them. Medical history revealed several surgical operations for female disorders, and she had been treated for thyroid gland trouble. History revealed an episode of severe psychic trauma, when, at the age of nine years, her uncle attempted to rape her. Following this episode, she developed an attitude of hatred toward most men. She was permitted out of the hospital on convalescent leave on one occasion, but was returned after a short period with symptoms of excessive religiosity. Following this return from furlough she deteriorated rapidly, became violent, combative, and had to be kept in restraint.

She was started on parenteral and oral reserpine, being given two injections of five mgm. approximately a month apart, and oral dosage was adjusted to five mgm. daily, at which level she obtained her optimum response. She is now out of restraint and helps in the ward, is neat and tidy in personal appearance, and attends social events. She recently went home on a Christmas pass and continued to improve during the eight-day period that she was out. She gained 11 pounds and her appearance improved considerably.

Case Abstract on S. F. (Parental Plus Oral)

Patient is a 29-year-old male Catholic college student who is single and has a history of eight months in mental hospital. Complaints on admission here, in March 1945, were nervousness, overactivity, depression, and crying spells. Background revealed the patient had had an apparently normal birth and early development. Family history revealed a maternal aunt who was in DePaul Hospital, New Orleans, La., three years, with a diagnosis of schizophrenia, he had a maternal cousin in a mental hospital. He was a third-year student at the Loyola School of Pharmacy at the time of his onset of mental illness in 1944. There is a history of two previous admissions to DePaul in 1944, with electroshock therapy and a remission for four months. Relatives felt that there were two episodes of psychic trauma which may have precipitated his mental illness. First, a rejection for military service, and, second, a recent disappointment in love. He was diagnosed as schizophrenic reaction, catatonic type, on his first admission here. Subsequently, he had a spontaneous remission in 1945 and was furloughed after nine months. Remission was only temporary, however, but he was kept at home where he remained seclusive and apathetic with little initiative, but was manageable. He was readmitted in 1952, at which time he was hallucinated, untidy, and uncommunicative. He showed a good response to seven electroshock treatments in 1952, which lasted only for seven months. He then relapsed with a rapid deterioration and was placed on an untidy back ward.

Reserpine was started Nov. 15, 1954, with an injection of five mgm. and oral dosage of one mgm. daily. Dosage was subsequently increased to six mg. daily, at which time optimum benefit was obtained. He became friendly, cooperative, neat, and tidy in personal appearance, and again began to visit and socialize with his mother, which he had not done previously for almost two years. No toxic effects were noted. His mother spontaneously expressed considerable satisfaction and pleasure at this unexpected improvement. He was subsequently allowed to leave the hospital on a pass, preparatory to convalescent leave.

Case Abstract on J. K. (Parenteral Plus Oral)

Patient is a 44-year-old white housewife who is married and has three children. She is Catholic in religion and has had a grade-school education. History reveals she has spent approximately 14 years in this hospital, entering at the age of 30. She had a short furlough within months after her first admission, but had to be returned to the hospital within a short time because of unmanageability and violence. Following her return, she had to be kept in almost constant restraint. There is a previous history of hospitalization in the state hospital at Williamsburg, W. Va., at which time she had made an abortive suicidal attempt by shooting herself through the right arm. Diagnosis at

Williamsburg was manic depressive-manic, which was changed here to paranoid schizophrenia. Background revealed an unhappy childhood, due to the fact that her parents separated when she was very young. She also had an unhappy marriage, in which her husband drank excessively and was brutal at times. Family history was negative for mental illness. She had a total of 319 electroshock treatments with no sustained improvement over 14 years.

At the time reserpine was begun, she was in full restraint, stamped on the floor, and beat the walls with her fist. She was also destructive and assaultive, and took no interest in her appearance or surroundings. She was given three 5-mgm. ampules of reserpine over a period of two months and oral dosage was adjusted at 6 mgm. daily. At the 6-mgm. level she attained her optimum response. She is now out of restraint, has become friendly, takes an interest in her personal appearance and has become more coherent and relevant. Her relatives express surprise and pleasure with her improvement, and she left the hospital on pass to have dinner and attend a movie for the first time in years.

Discussion

Effect on blood pressure. The hypotensive effect ascribed to reserpine (Robert W. Wilkins, 1954) was clearly demonstrated in our study. It was our impression in the observation of 55 patients receiving parenteral injections that each patient had his own consistent specific reaction pattern of blood-pressure response. Once this reaction was established by careful observation, we did not feel the need for the close observation used initially in subsequent injections. We found that the maximum drop in blood pressure occurred in the first four hours. In several cases, however, the blood pressure at the end of the 24-hour period was slightly lower than at the end of the first 4-hour period. We noted, in several patients who had their maximum blood pressure drop at the end of 24 hours to a low level, that another injection was followed by a subsequent rise in blood pressure rather than by a continued drop. Apparently, the reserpine exerts its maximum effect on the blood pressure, reaching a base line beyond which there is no further response. Oral reserpine alone also was shown to decrease blood pressure in our study (see TABLE 2), but the effect was a gradual one occurring over a period of several days. We noted, in several patients receiving oral medication, that a parenteral injection caused no further drop in blood pressure. We also noted that a higher dosage level of oral reserpine had no further effect on blood pressure, once a response had occurred in those already on oral medication.

Toxicity. We were impressed by the apparent lack of toxicity of reserpine in our entire series. We noted a few minor complaints such as nasal stuffiness, muscle aches, slight diarrhea, moderate apathy, and increased dreaming. We continued the same dosage, however, in spite of these effects, and they all disappeared within two or three weeks with the exception of the increased dreaming. Two cases in our parenteral group experienced blood pressure drops to 80/54 and 78/54 from slightly above normal pressures. They were given ephedrine and wyamine, resulting in a gradual rise of blood pressure towards normal. These cases occurred early in our series, and subsequent observation of other similar drops with no sign of shock has convinced us that these two could have safely gotten along without the vasopressors. An injection of five mgm. of reserpine i.m. in some patients had no apparent initial effect, whereas subsequent injections produced a marked circulatory and/or a tranquilizing response. Apparently, there is a wide variability of individual response and each patient has his own optimum dosage level.

Method of administration. Oral administration of reserpine plus shock produced the highest percentage of marked improvement in our study (see TABLE 7). Parenteral plus oral, however, appears to be the treatment of choice in patients who are electroshock therapy risks. We feel that oral reserpine can be used safely in treating outpatients but, if parenteral is added to the therapeutic regime, the patient should be placed under close observation until his reaction pattern of blood-pressure response is established.

Effect on psychic states. A definite quieting and tranquilizing effect resulting from the administration of reserpine was noted in our study, without apparent habituation or addiction. Some of the patients, however, did develop a strong psychological dependence on the drug. Reserpine did not appear to change the mental processes in many cases, but there was improved relevance and coherence in some patients, with no change in their delusional systems. In others, the psychotic process apparently was changed or reversed, with a disappearance of the delusions and hallucinations. A significant number of patients became better integrated and more amenable to therapy of all types. Reserpine was found to be particularly useful in those patients in which electroshock therapy was contraindicated, as in cases of pulmonary tuberculosis, hypertensive cardiovascular disease, organic brain disease, *etc.* It was observed to produce a decrease in choreiform or choreoathetotic tremors in several patients. Further study is indicated to learn if it has a permanent beneficial effect in these extrapyramidal tract disorders. An unusual response was noted in a case of Huntington's chorea, which is described as follows:

A far-advanced case of Huntington's chorea, with constant threshing and choreiform movements, was treated by the senior author. The patient showed no response to the first five mgm. injection, but quieted markedly with the second injection of five mgm. on the third day. He received 20 mgm. over a period of seven days and, on the seventh day, his rectal temperature dropped to 94.4, respiratory rate to seven and blood pressure to 90/50. His respirations were extremely deep and somewhat sighing, but he did not appear to be in any severe distress. Pulse rate was 50 per minute and regular, but weak. Subsequent injections of coramine and adrenalin raised the patient's blood pressure to 110/80 and respirations to 12 per minute within next two to four hours. Pulse did not change markedly, increasing to 62. The drug produced a marked quieting effect on the patient and a marked reduction in his restlessness and choreiform movements. He also became more cooperative and attempted conversation with the attendants and with the author, an action he had not initiated previously, at any time.

Out of 164 patients receiving reserpine, 67 were affected as follows: 32 were transferred to better wards; 23 were able to leave on pass, and 12 were furloughed (released on convalescent status).

Many patients who improved, but were unable to leave, became assets to the hospital and were able to take care of themselves. Some performed useful functions in the ward or worked in some productive capacity in other areas. The cost of the medication daily per patient is negligible when one considers the savings resulting from a reduction of (1) materials destroyed by violent patients; (2) number of attendants necessary to manage a violent, untidy, chronic, or TB ward; and (3) the extra medical care necessary for patients injured by assaults.

It was also noted by attendants and supervisors that violent wards became quiet and easier to manage and were no longer considered as violent wards. Several excited or irritable patients can touch off a whole ward and produce mass excitement. Rationale of therapy was to treat first the worst patients having recurrent episodes of excitement, and gradually increase the scope of the medication to include the next most irritable, *etc.*

Summary and Conclusions

Two hundred and nine patients, divided into five groups and including three additional cases, were treated in this study. The first 4 groups were treated for 45 days, the fifth group for 2 months. One hundred and sixty-four patients received reserpine in the entire group. There were 2 control groups consisting of 45 patients. Response of all but the 39 patients in our epileptic group was graded, using an index of marked, moderate, slight improvement, and no change categories. The epileptic group was graded in response to reduction in seizure frequency. Each group was discussed and evaluated separately.

Final Summary:

Group I. Eleven acutely disturbed patients, 100 per cent improvement to some degree.

Group II. Thirty-nine chronic epileptics, statistically significant reduction in seizure frequency at 2 to 5 per cent level. Controls, no change in seizure frequency.

Group III. Twenty-two chronic patients, 83 per cent improvement to some degree.

Group IV. Twenty-four TB patients, 83 per cent improvement.

Group V. One hundred and ten supplementary mixed group, 73 per cent improvement. Controls, 8 per cent improvement in group.

(1) Reserpine was effective as an adjunct in treatment of epilepsy, and it may be effective in the treatment of status epilepticus.

(2) Oral (or parenteral plus oral) combined with shock is dramatically effective in a wide variety of mental disorders, many with long duration of illnesses.

(3) Reserpine appears to be beneficial as an adjunct in treatment of extrapyramidal tract disorders. Further research is indicated as to the action of reserpine, particularly in the treatment of extrapyramidal tract disorders and its effects on the electroencephalographic tracing.

(4) Sixty-seven patients were able to leave the hospital on furlough or pass, or were transferred to better wards.

(5) Parenteral plus oral treatment of psychotic tuberculosis cases produced

dramatic results in some cases, with improvement of the underlying disease process.

(6) Reserpine may prove useful to the electroencephalographer in reducing the muscle artifact resulting from involuntary tremor in those cases in which EEG is desired.

(7) Reserpine appears to have an extensive area of usefulness in the treatment of a wide variety of psychiatric disorders.

Acknowledgments

Grateful appreciation is expressed to Doctor E. M. Robards, Superintendent, and the entire medical staff of the East Louisiana State Hospital for their valuable assistance and cooperation in carrying out this research study. We also wish to thank Doctors Robert A. Matthews, Professor of Psychiatry, and Richard A. Paddison, Associate Professor of Neurology at the Louisiana State University School of Medicine, for their helpful suggestions.

Further appreciation is expressed to Lorenzo Smith, Business Administrator of the hospital, and to Mrs. Erlene Wilcox, R. N., and to Mr. & Mrs. Nathan Manuel for their cooperation and invaluable assistance in this project.

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CLINICAL AND PSYCHOLOGICAL OBSERVATIONS ON PSYCHIATRIC PATIENTS TREATED WITH RESERPINE: A PRELIMINARY REPORT*

By Jay L. Hoffman and Leon Konchegul
George Washington University School of Medicine and Saint Elizabeths Hospital, Washington, D. C.

A considerable number of psychiatrists are prejudiced against the use of drugs in the treatment of psychological illness. In part, this prejudice is based on the widespread use, or abuse, of the sedative and hypnotic drugs. These medicaments have been aptly described as representing "chemical restraint" and, when they are so used, they are subject to all the objections made against mechanical restraint of the mentally ill.

Sharing the prejudice above referred to, the authors were impelled to determine for themselves, with as much objectivity as they could muster, whether the drug reserpine (Serpasil) is, in fact, a generically different therapeutic agent than the hypnotic drugs and whether it has the effects desired for our patients. Although this is only a preliminary report of a seven-week period of observation, and although there are still certain details regarding the use of this drug about which we expect to learn more, we believe that we can properly answer both of these questions in the affirmative.

Selection of Patients. Five groups of patients, from as many different services in the hospital and numbering 20 or 24 in each group, were selected by their respective Chiefs of Service. The total number studied was 108. All were psychotic, and the criteria for their selection were, essentially, that they be the most restless, disturbed, agitated, combative, or destructive patients on the service. One of the five groups selected was from our Geriatrics Service.

The Geriatric Service patients varied in age from 51 to 91, with a median age of 73. The others varied from 18 years of age to 60, with a median of 35. Most of the geriatric patients were diagnosed as suffering from either senile psychosis or psychosis with cerebral arteriosclerosis. Seventy of the 88 patients in the other four groups carried the diagnosis of schizophrenia. The period of hospitalization for the entire group extended from 3 months to 21 years, the median being between 2 and 3 years. There were 41 women and 67 men. Both white and Negro patients were included.

Plan of Study. The patients in each of the five groups were "stratified" into two comparable sections, based on age, diagnosis, length of hospitalization, and the designation, by the Chief of Service, of those who were most and those who were least disturbed.

The study is divided into three seven-week periods. For the first period, the members of one section of each of the five groups received reserpine, and the members of the second section received placebo. For the second period, the medications were reversed. For the third period, those receiving reserpine at the end of the second period continued to receive it for 7 more weeks, making a total of 14 weeks of active drug administration for these patients. Those receiving placebo at this time received nothing for the third period. None but the authors knew which medication was the active drug.

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* Reserpine (Serpasil) for the work described in this paper was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

This report deals only with the clinical observations made during the first seven-week period.

Plan of Dosage. One physician on each service* was responsible for the supervision of the study on his service, including the determination of the daily doses of medication. The general plan was to begin with 2.0 mgm. daily by mouth or, if refused, to give 2.5 mgm. intramuscularly (i.m.). This minimum dose, with a few exceptions, was continued throughout. On the third day 2.5 mgm. i.m. was added and, thereafter, the dose was increased at three-day intervals by increments of 2.5 mgm. i.m. daily until the desired "tranquilizing" effect was reached, or until a total dosage of 9.5 to 10.0 mgm. was reached, whichever came first.

The dose thus reached was either continued or reduced, depending on the patient's symptomatic response. In most instances, the intramuscular medication was partially or completely replaced by the oral form as the patient became more cooperative.

The range of dosage most common after the first week was between 5.0 and 10.0 mgm. daily.

For the geriatric patients, an elixir containing 1 mgm. reserpine per 4.0 cc. was used, and the maximum dosage was 6.0 mgm. daily.

All of the medication was given once daily, in the morning. All other medication, particularly sedatives, was discontinued at the beginning of this study.

Plan of Observation. Observations were made and recorded by psychiatrists, nurses, and a psychologist. With but few exceptions, each of these workers made his observations on the same group of 4 to 6 patients throughout the period of study. In all, 18 psychiatrists, approximately the same number of nurses, and 1 psychologist contributed their observations.

The following examinations or tests were carried out on all patients immediately before medication was begun: Bellevue-Wechsler and Rorschach Tests (by the psychologist), Lorr Multidimensional Scale for Psychiatric Patients (one by the nurse and one by the psychiatrist), a comprehensive mental status examination by the psychiatrist, and a detailed description of ward behavior by the nurse. The latter two were repeated weekly throughout the study. The others were repeated once during the 7th week and again during the 14th week.

Observations. An objective and accurate evaluation of treatment in psychiatry is difficult to achieve. Observations are made by people exercising their individual judgments, relying on past experience, making automatic comparisons, and arriving at evaluations. These observations are then reported as figures and percentages, and are promptly accorded, by many, a precision that the facts of their origin do not often warrant.

Because, in general, each psychiatrist and nurse made and recorded observations on not more than four to six patients, considerable detail was possible.

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* Doctors Neil C. Waldrop, Leon J. Epstein, Robert H. Robertson, Michael A. Woodbury, Isabelle R. Schaffner, to all of whom—and to the many others who participated—we wish to express our indebtedness.

Also, the observers were not likely to develop any strong emotional investment in the results of the study. Furthermore, in 4 of the 5 groups, not more than 12 patients on wards of 40 to 60 patients received the active drug at any one time. This, we believe, reduced the "reverberating" effect that improving patients have on one another, on the ward as a whole, and on the ward personnel. In other words, symptomatic improvement was more properly attributable to the effects of the drug *per se* than to the drug plus improvement in the ward "climate."

Physicians and nurses were encouraged to evaluate the effects of medication at the end of 7 weeks in terms of "slight," "moderate," and "marked" improvement of behavior, using whatever criteria of improvement they deemed appropriate. In addition, one of the authors (J. L. H.) read all of the detailed weekly notes of behavior made by both psychiatrists and nurses and made a similar and independent evaluation. There was general agreement in all these evaluations. On this basis, 38 out of 52 patients (73 per cent) receiving reserpine for 7 weeks showed some degree of improved behavior. Breaking this figure down, it is found that: 17, or 33 per cent, showed slight but definite and sustained improvement; 14, or 27 per cent, showed moderate and sustained improvement; and 7, or 13 per cent, showed marked and conspicuous improvement.

In the group of 53 patients who received placebo for 7 weeks, only 3 patients (5+ per cent) showed any degree of sustained improvement. Of these 3, 2 patients showed slight, and 1 patient showed moderate improvement. None showed marked improvement.

During the period of study, 3 of the geriatric group—2 who had received reserpine and 1 placebo—died of causes unrelated to the administration of the medication.

A study was made of the number of patients in seclusion, and the total number of hours so spent, for the seven-week period immediately preceding the administration of the medications as compared to the same length of time during which medication was given. For those patients receiving reserpine, 24 spent a total of 12,830 hours in seclusion before medication, while 18 were secluded 7,057 hours during medication. This represents a reduction of 45 per cent in the total number of seclusion hours.

For the patients receiving placebo, 27 patients spent a total of 13,115 hours in seclusion before, while 21 were secluded for 10,782 hours during medication. This, too, represents a reduction, but of 18 per cent (as compared to 45 per cent).

We do not ordinarily use mechanical restraint anywhere in the hospital except in one double ward of our Maximum Security Section. Most of the patients here are also prisoners; they include a small proportion who are impulsively and unpredictably assaultive and this to a major degree. In this section, those patients receiving reserpine showed a reduction of hours in restraint from 4 patients and 3374 hours to 3 patients and 1916 hours, a *reduction* of 1458 hours, representing 43 per cent of the total hours spent in restraint during the 7 weeks immediately preceding the medication period. The group receiving placebo showed an *increase* of hours in restraint of nearly 10 per cent (from 4 patients and 3321 hours to 4 patients and 3630 hours).

The reduction in restraint hours is all the more remarkable if one understands that such patients have been greatly feared by ward personnel because of their previously violent behavior. Some of these patients have been in restraint for extended periods of time prior to receiving reserpine. It is to be expected that ward personnel, as well as physicians, would be very slow in releasing them from restraint. Otherwise the comparative figures in this group might have been even more impressive.

The number of accidents and injuries in both groups was too small to be used as an index of change.

Side Effects

(1) *Torpor*. We have used this term in preference to "drowsiness," although neither seems to express quite what we have observed. What is observed in such patients seems to represent a motor slowdown rather than a psychic slowdown. The patient is readily aroused and, when aroused, seems quite alert mentally. His conversation is spontaneous and to the point, and he does not give the observer the impression of being a sleepy person. If asked to do so, such a patient will participate effectively in, *e.g.*, a volleyball game. This sign (*i.e.*, torpor) is reminiscent of the somnolence seen in patients with slow-growing pituitary tumors.

In our experience, about three fourths of the patients who show an over-all favorable response to reserpine display some degree of torpor. It usually continues in evidence in these patients during the period when the dosage of reserpine is at the level of 7 to 10 mgm. a day. Generally, it becomes less evident in the evening (when the medication is given in a single morning dose).

(2) *Chilliness* (*or tremulousness*). This feeling did not occur very frequently, but patients who did experience it disliked the sensation. They describe it as being different from the feeling that accompanies a "cold," nor do they feel cold when it occurs. Some speak of it as "nervousness." Some seem to be quite anxious, and one wonders whether this experience represents free-floating anxiety no longer "bound" to the psychotic patient's abnormal mental content or expressed in disturbed behavior. The symptom usually lasts 10 to 15 minutes and passes away spontaneously, but may recur. It is not associated with either fever or fall in blood pressure.

(3) Other side effects included considerable nasal congestion, some diarrhea, some puffiness of the face and edema of the feet, and one case of a Parkinsonian-type syndrome. The latter is clearing up with a reduced dosage of reserpine.

General Considerations

The patients here considered—before medication—were restless, agitated, confused, assaultive, and combative. The number who required seclusion was relatively high. Many were hostile, suspicious, tense, and threatening. They included the untidy, the incontinent, the markedly regressed patients who refused to wear clothing or who smeared themselves and their surroundings with feces. They did not, as a rule, participate in the activities available to them, nor could they associate with their fellows without conflict. Many were hallucinated or delusional or both. They were noisy, destructive, resistive, angry, obscene, vulgar, vituperative.

After receiving reserpine, 27 per cent showed little or no change. This is in itself a point of differentiation from the common hypnotic drugs. The latter, with a single dose of the appropriate drug, will almost always produce the expected effect promptly.

For the 73 per cent who showed some degree of improvement, the most common observation was a reduction of motor hyperactivity, of tension, of hostility, and aggressiveness. Seclusion became less frequent or was eliminated. Patients who had not previously worn clothes now did so. Those who had been untidy or careless in their dress now took more interest in their personal appearance. Communication with some of the patients became easier, and their speech became more coherent and less confused. They found it easier to talk about their delusions and hallucinations. While most, if not all, retained their abnormal content, they seemed to be made less anxious by it. Sometimes, if they were willing to discuss their delusions or hallucinations at all, they gave the impression that their abnormal ideas were actually not their own but rather those of a third person.

Those who showed the most marked degree of improvement became affable, bland, friendly. They asked to be given ward work to do, and began talking about when they could go home. They participated again in recreational activities, played checkers and cards, took part in ball games, went for walks, watched television programs, and read newspapers and books.

The effect of such patient improvement on the morale of the ward personnel was noteworthy. In one ward, where the reserpine was reserved for the patients included in this study, an over-active boy had been given some of the drug by a physician who had begged of his colleagues all the samples they had. When no more samples were forthcoming and the boy was again becoming disturbed, the nurses agreed among themselves to take up a collection to buy more of the drug for this patient. Needless to say, the hospital took appropriate action to make this action unnecessary.

Comments

So far as we know, this is the first time that we have had available a drug that significantly reduces motor excitement and many of its common accompaniments of behavior, without at the same time producing confusion, lethargy, and deep sleep. The hypnotic drugs, as commonly used, made more definitive and lasting therapy impossible. This drug *demands* that every other therapeutic resource available be used intelligently in the further treatment of our patients, for the patients who respond to reserpine are now more accessible to such therapy (this probably includes also those receiving intensive individual psychotherapy, if our experience with one patient receiving such treatment is any indication).

Rather than solving the difficult problems of the hospital treatment of the mentally ill, the availability of a drug such as this introduces grave problems for the conscientious hospital administrator, psychiatrist, and nurse. We believe it will be found that while the burdens of caring for the disturbed are lessened by reserpine, the challenge of providing appropriate additional psychiatric treatment for those no longer disturbed will tax all of our ingenuity, skill, and resources.

It seems reasonable to recommend that no patient should be considered for psychosurgery until he has first been given a trial with this drug. With the possible exception of depressed patients, the same statement probably applies to electric shock therapy.

The period of observation covered by this report is a relatively brief one. The authors find themselves still with a number of incompletely answered questions. We do feel strongly, however, that we must not be content with bringing a drug-induced "tranquility" to our patients but, rather, that we must seize the opportunity provided by such "tranquility" to give our patients the best additional psychiatric treatment our resources permit.

THE ACUTE EFFECTS OF RESERPINE AND OF AMYTAL ON CENTRAL SYMPATHETIC REACTIVITY*

By Robert A. Schneider

Departments of Medicine and of Psychiatry and Neurology, University of Oklahoma School of Medicine and University Hospitals; and The Oklahoma Medical Research Foundation, Oklahoma City, Okla.

There is presumptive evidence that the alkaloid, reserpine (Serpasil), is a central nervous system depressant which acts primarily at a subcortical level.[1, 2, 3, 4, 5, 6] Prolonged administration of reserpine is often accompanied by decrease in body temperature, decrease in metabolic rate, and a type of drowsiness from which the subject can be readily aroused. These findings, together with evidence that this drug leads to alteration in autonomic balance, have suggested that reserpine affects autonomic balance at a central level, possibly in the hypothalamus and the medullary centers. The present study was designed to determine the action of reserpine and of Amytal on central sympathetic reactivity (C.S.R.) using Funkenstein's Mecholyl^R test,[7] the validity of which will be discussed.

Methods

The Funkenstein test was conducted on 10 ambulatory patients (8 male and 2 female, ages 24 to 62 years), selected from a medical service. Three had essential hypertension. The remaining were normotensive and were suffering from such disorders as rheumatoid arthritis, diabetes, and peptic ulcer, and one had severe postural hypotension secondary to multiple sclerosis.

The Funkenstein test was conducted in the following manner. The patient reclined comfortably on an examining table for a minimum period of 20 minutes, and the blood pressure was recorded each minute during the last 5 minutes. When a stable blood pressure level had been established, 10 mg. of Mecholyl chloride was injected subcutaneously, and the blood pressure taken every minute thereafter for a standard period of 25 minutes. The blood pressures were plotted against time, and the degree and duration of hypotensive response was established. The area of hypotension and the number of minutes required for the blood pressure to re-establish at the preinjection level ("homeostasis") constituted the essential features of the test. FIGURE 1 illustrates diagrammatically the three principal blood pressure patterns that are possible after Mecholyl together with Gellhorn's[8] neurophysiologic interpretation based on animal experimentation. *Normal* central sympathetic reactivity is characterized by a moderate fall in blood pressure with a return to preinjection levels within 10 to 12 minutes and without overshooting. *Decreased* sympathetic reactivity is present when there results a marked fall in blood pressure and a failure to re-establish homeostasis within the standard 25-minute period. A modest fall in blood pressure with a prompt return to baseline values and an "overshooting" is characteristic of *increased* central sympathetic reactivity.

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* The research reported here was aided in part by a grant from Ciba Pharmaceutical Products, Inc., Summit N. J., who also provided the reserpine (Serpasil) used in this study.

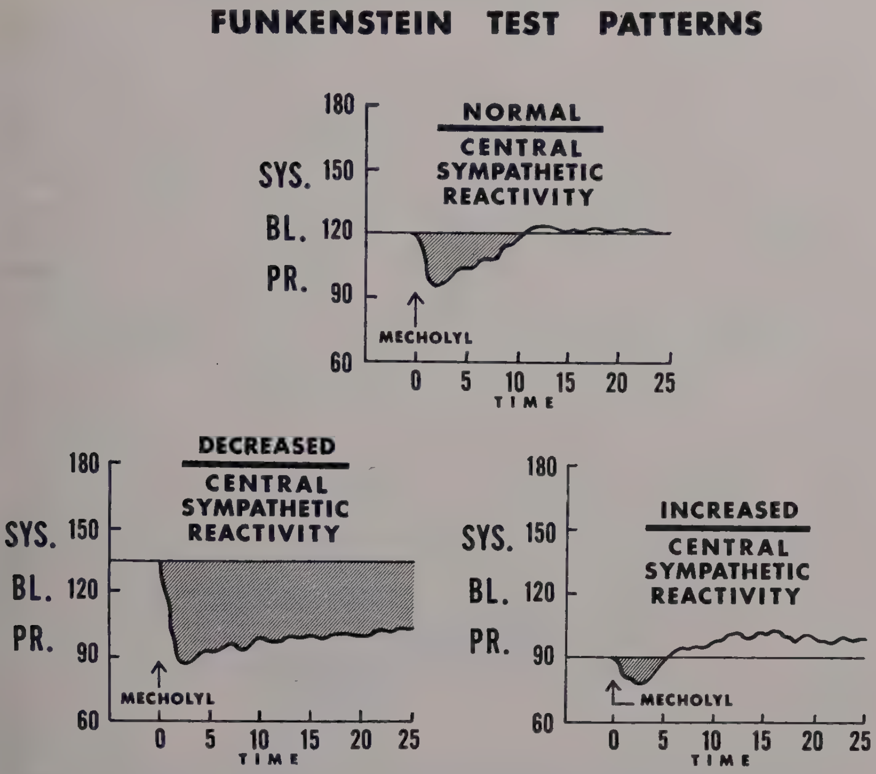

FIGURE 1. A schematic representation of the three prototype blood pressure response patterns after Mecholy l (Funkenstein test) together with Gellhorn's neurophysiological interpretation for each.

Each subject was given the Mecholyl test on three different days, once without premedication, to establish that subject's control pattern; once after the administration of reserpine (five subjects were given 1.0 mg. reserpine orally one hour before the test, four were given 2.5 mg. reserpine intramuscularly (i.m.) three hours prior to the test, and one subject was tested after having been on 0.75 mg. reserpine daily by mouth for one week); and again, on a different occasion, after Sodium Amytal administration (250 mg. orally one hour before testing in five subjects, 250 mg. i.m. two hours prior to testing in three subjects). The control pattern was taken to reprcsent the subject's usual central sympathetic reactivity (C.S.R.). The curve after reserpine was interpreted as representing the C.S.R. as influenced by reserpine, and it was designated as showing increased or decreased C.S.R. as compared to that subject's control pattern. In a subject who showed an increased C.S.R. on the control test, the Mecholyl pattern after reserpine was interpreted as showing decreased C.S.R. if the pattern changed toward that of normal C.S.R. The same interpretations were placed on the curves obtained after the administration of Sodium Amytal.

TABLE 1

RESULTS OF FUNKENSTEIN TEST (MECHOLYL) C.S.R. WITHOUT PREMEDICATION, AFTER RESERPINE AND AFTER AMYTAL

Subject	Sex	Age	Control		Reserpine			Amytal		
			Baseline B.P. (mm.)	Central sympath. reactivity	Dose/route time (hrs.)	Baseline B.P. (mm.)	Central sympath. reactivity	Dose/route time (hrs.)	Baseline B.P. (mm.)	Central sympath. reactivity
F. T.	M	43	112	Normal	1.0 mg./p.o. 1	121	Decreased	250 mg./p.o. 1	118	Decreased
S. S.	M	50	106	Normal	1.0 mg/.p.o. 1	85	Decreased	250 mg./p.o. 1	95	Decreased
I. C.	F	29	145	Normal	2.5 mg./i.m. 3	142	Decreased	250 mg./i.m. 2	148	Decreased
T. J.	M	21	126	Increased	1.0 mg./p.o. 1	117	Decreased	250 mg./p.o. 1	119	Decreased
S. E.	M	62	114	Increased	2.5 mg./i.m. 3	106	Decreased	—	—	—
B. L.	M	54	181	Increased	0.75 mg./p.o. daily—1 week	186	Decreased	—	—	—
P. L.	M	56	115	Decreased	2.5 mg. i.m. 3	112	Increased	250 mg./i.m. 2	108	Decreased
H. N.	M	55	124	Decreased	1.0 mg./p.o. 1	100	Increased	250 mg./p.o. 1	106	Decreased
E. S.	M	42	116	Decreased	1.0 mg./p.o. 1	95	Increased	250 mg./p.o. 1	112	Decreased
D. N.	F	58	152	Decreased	2.5 mg./i.m. 3	145	Decreased	250 mg./i.m. 2	120	Increased

Results

The results of the Funkenstein test, in terms of central sympathetic reactivity in the 10 subjects obtained under control conditions, after reserpine and after Sodium Amytal are summarized in TABLE 1. Also indicated are the baseline blood pressure levels in each case, and the dosage, route of administration, and time interval for reserpine and Amytal in each case.

(1) *Central sympathetic reactivity without prior medication* (*control patterns*). It is evident from the table that C.S.R. is not always "normal" in unselected subjects. Of the 10 subjects, 3 showed normal C.S.R., 3 had increased C.S.R., and 4 showed decreased C.S.R. Of the 3 hypertensive subjects, 1 had normal, 1 increased, and 1 had decreased C.S.R. at the time of measurement. The 6 normotensive subjects had a similar distribution of C.S.R. patterns. The patient with postural hypotension (E. S.) showed the pattern of decreased sympathetic reactivity.

(2) *Central sympathetic reactivity following the acute administration of reserpine.* Reference to the appropriate column in TABLE 1 will indicate the C.S.R. patterns which accompanied the acute administration of reserpine. In 8 of the 10 subjects, the average baseline blood pressure values, prior to adminis-

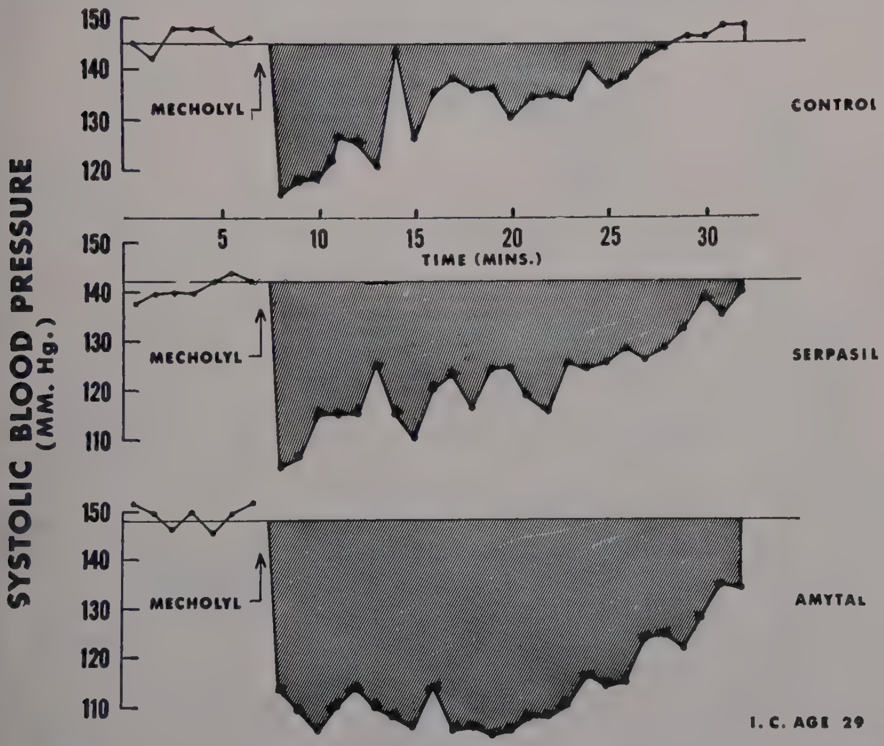

FIGURE 2. The three Funkenstein test patterns obtained in subject I. C. (see TABLE 1), who showed *normal* C.S.R. under control conditions (top diagram). The middle diagram shows decreased C.S.R. following reserpine The bottom diagram shows the decreased C.S.R. after Amytal.

tration of the test dose of Mecholyl, averaged 12 mm. Hg less than control baseline values. There appeared to be no significant difference in the hypotensive effect of reserpine when 1.0 mg. was given by mouth as compared to 2.5 mg. given i.m. A nearly consistent pattern of change in C.S.R. occurred following the administration of reserpine with only one subject showing a deviant pattern (D. N. in table 1, who had had a bilateral thoracolumbar sympathectomy three years ago). It was found that the change in C.S.R. (a tendency for increase or decrease) depended on the subject's control C.S.R. Those subjects who, under control conditions, showed normal or increased C.S.R. (first six subjects in table 1), showed *decreased* C.S.R. following the administration of reserpine. Figure 2 (subject I. C.) shows the typical patterns seen in a patient who begins with normal C.S.R. Figure 3 (subject T. J.) illustrates the typical blood pressure patterns for a patient who begins with a control pattern indicative of central sympathetic overreactivity. Subjects who show decreased C.S.R. without premedication, however, have *increased* C.S.R. after reserpine. This was true for three of the four subjects with control patterns of decreased C.S.R. Figure 4 (subject E.S.) illustrates a representative example of this group. The last subject in table 1, although showing

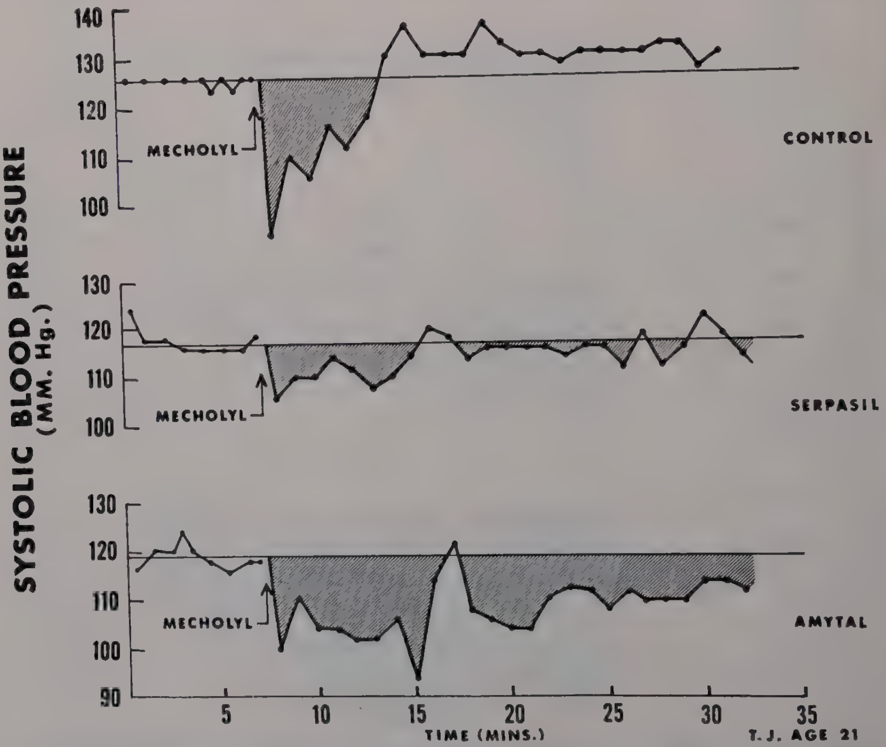

Figure 3. The three Funkenstein test patterns for subject T. J. (see table 1) which is representative for those subjects who show *increased* C.S.R. under control conditions. The middle diagram shows the decreased C.S.R. (relative to the control response) following reserpine. The bottom diagram shows the decreased C S.R typicallyseen after Amytal.

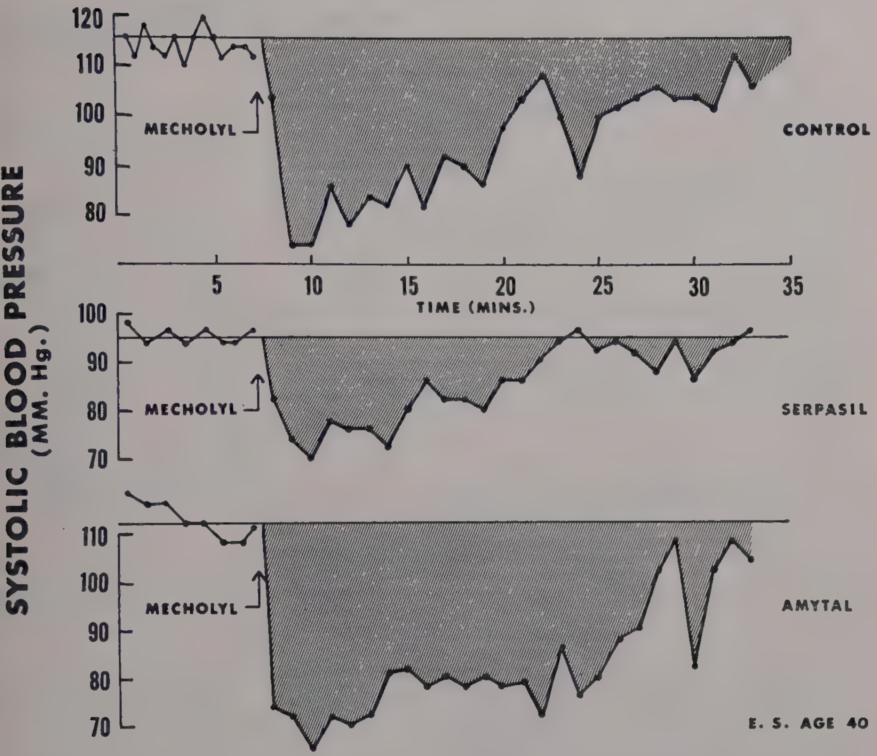

FIGURE 4. Funkenstein test patterns for subject E. S. (see TABLE 1), representative of those patients who, without prior medication, show *decreased* C.S.R. Note in the middle diagram that following reserpine there was evidence for increased C.S.R. The bottom diagram again shows the usual decreased C.S.R. which follows Amytal.

decreased C.S.R. under control conditions, showed decreased C.S.R. after reserpine. This is the subject who had had the prior Smithwick procedure.

Of special interest was subject E. S., who suffered from severe postural hypotension secondary to multiple sclerosis. Since there is a general consensus that, in such cases, the hypotension is due to central sympathetic *under*reactivity,[9] this subject's response to reserpine was of special interest. In FIGURE 5, blood pressure response to change in posture in this patient is diagrammed, first without premedication (interrupted line) and, on another occasion, after receiving 1.0 mg. reserpine *per os* (p.o.) one hour before the test (solid at 90° line). The control test shows the hypotensive postural response, most marked where, at one point, his blood pressure was unobtainable. Following administration of reserpine, it will be seen that the fall in blood pressure is less marked, especially at 45°, and that, at 90°, the blood pressure was obtainable at all times and was at a somewhat higher level. This suggests, again, increased C.S.R. following reserpine in a subject with decreased C.S.R. under control conditions, and it parallels the Funkenstein test findings in this same patient (E. S. in TABLE 1), where reserpine was also accompanied by increased C.S.R.

(3) *Central sympathetic reactivity following the acute administration of Sodium*

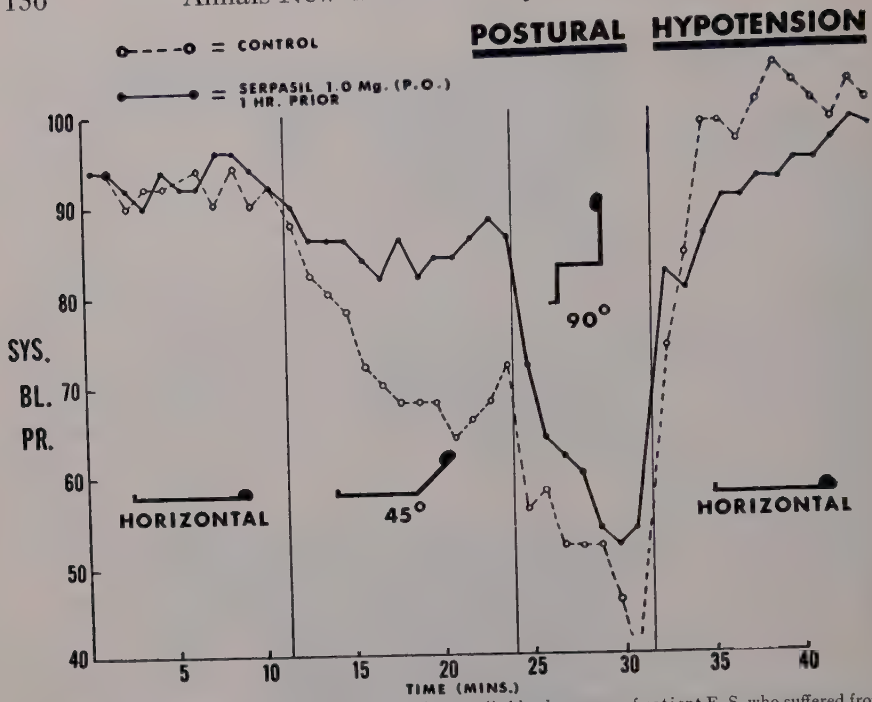

FIGURE 5. Illustrated is the effect of gravity on the systolic blood pressure of patient E. S. who suffered from postural hypotension. The interrupted line shows the response on a day when the subject had had no premedication. The solid line represents the response on another occasion one hour after the administration of reserpine (see text)

Amytal. Reference to TABLE 1 will show that the basal blood pressures, after Amytal, were lower than the control basal pressures in the six of the eight subjects who received Amytal, and the decrease averaged 13 mm. Hg, which was a similar decrease to that seen after reserpine. Seven of the eight subjects receiving Amytal showed a decrease in C.S.R. and, in contradistinction to the administration of reserpine, the decrease was unrelated to the control C.S.R. in these subjects. This finding is in agreement with the reports of decreased C.S.R. after Amytal of other investigators.[8] The bottom curves in FIGURES 2, 3, and 4 illustrate the consistent pattern of decreased C.S.R. after Amytal. The only subject showing increased C.S.R. after Amytal was the last subject in TABLE 1 (D. N.), the patient who had had the Smithwick procedure.

Discussion

Gellhorn's observations[8] on anesthetized cats receiving Mecholyl are pertinent to the interpretation of the Funkenstein test and to an understanding of our findings. Gellhorn states that any procedure leading to a fall in blood pressure of significant magnitude (such as that produced by Mecholyl) induces a sympatheticoadrenal discharge through a fall in blood pressure in the sino-aortic area and through a central sympathetic reflex which tends to counteract the hypotension. He used the normally innervated nictitating membrane tc indicate a sympathetic discharge and the acutely denervated nictitating membrane to measure adrenomedullary secretion. The left-hand side of FIGURE 6 shows that Mecholyl induces sympatheticoadrenal discharges. The sympathetic response (innervated nictitating membrane) begins when the Mecholyl-induced fall in pressure is considerable and accounts for the quick return of blood pressure. The second slow phase in return of blood pressure appears to coincide with the humoral phase (denervated nictitating membrane). The bigger the dose of Mecholyl, the greater the responses and the more prolonged the hypotension. Note that the nictitating membrane responses to intravenous adrenalin are similar to those resulting from Mecholyl. If it is true that Mecholyl elicits a reflex excitation of centers of the sympatheticoadrenal system, *direct stimulation* of the centers may be expected to induce similar changes. These changes are illustrated on the right-hand side of FIGURE 6. On stimulation of the medullary sympathetic center (also true of the hypothalamus), a sympathetic response is followed by a humoral response. This is similar to that induced *reflexly* by Mecholyl.

In FIGURE 7 (left-hand side) is illustrated the effect of tetraethylammonium (TEA). TEA blocks autonomic synapses, although it does not interfere with the reactivity of peripheral effectors. Thus, *reflexly induced* activation of sym-

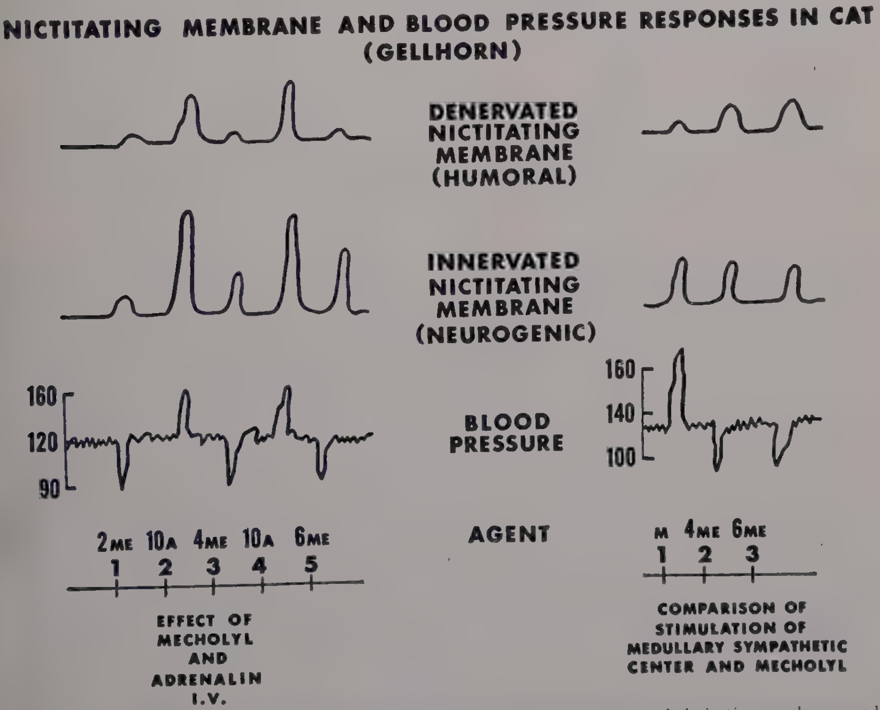

FIGURE 6. Left side of figure shows the response of the denervated and innervated nictitating membranes and blood pressure in the cat to the intravenous injection of Mecholyl (ME) and of adrenalin (A) in micrograms. Right side of fig. shows the response of the same indicators to stimulation (M) of the medullary sympathetic center as compared to the action of i.v. Mecholyl (ME) (see text). This figure and FIGURE 7 are reproductions of figures from E. Gellhorn's *Physiological Foundations of Neurology and Psychiatry*, 1953, by permission of the publisher, the University of Minnesota Press, Minneapolis, Minn.

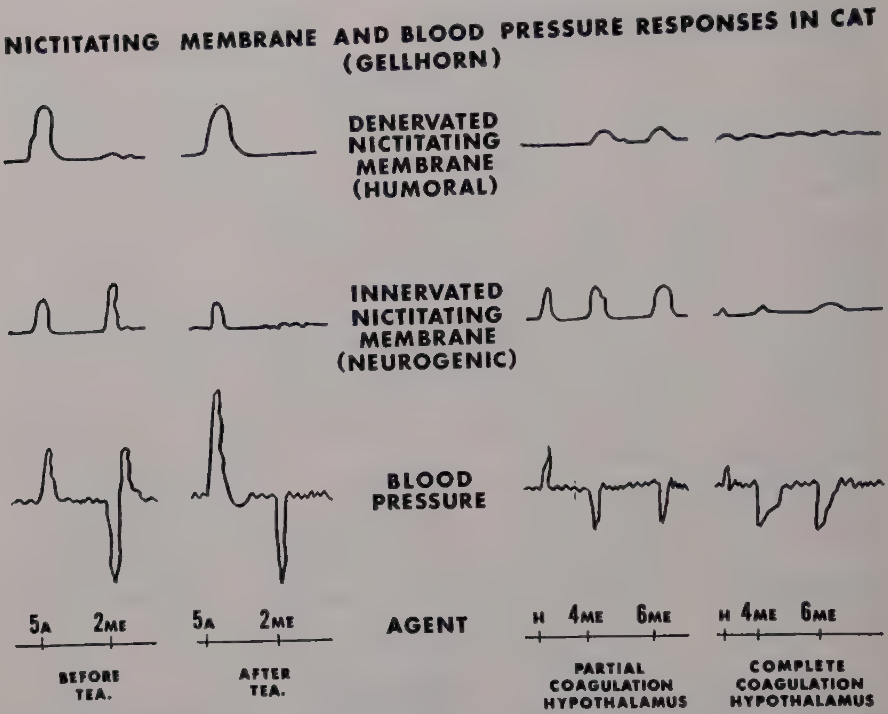

FIGURE 7. Left side of figure shows the response of the nictitating membranes and blood pressure in the cat to the intravenous injection of adrenalin (A) and Mecholyl (ME) before and after the administration of tetraethylammonium chloride (TEA). On the right is shown the effect of partial and complete coagulation of the posterior hypothalamus on the action of direct stimulation (H), and Mecholyl (ME) (see text).

pathetic and parasympathetic centers may be reduced or abolished by TEA. TEA diminishes or eliminates sinoaortic reflexes. Thus, the increased pressor response to intravenous (i.v.) adrenalin after TEA. The reactivity of peripheral structures (the nictitating membranes) is unchanged (reaction of nictitating membranes to adrenalin are unchanged). The action of Mecholyl, is changed fundamentally, however. The marked sympatheticoadrenal reaction before TEA to Mecholyl *fails* to do so after TEA. Thus Mecholyl elicits a sympatheticoadrenal discharge through *reflex* stimulation of autonomic *centers*. Also, it was found that the degree of hypotensive action of Mecholyl is indirectly related to the intensity and duration of the sympatheticoadrenal discharge. The right-hand side of FIGURE 7 shows the effect of coagulation of the posterior hypothalamus on the action of Mecholyl. There is good evidence that a fall in pressure in the sinoaortic area evokes an increased sympatheticoadrenal discharge via the sinoaortic nerves. The participation of the hypothalamus in this reaction initiated by Mecholyl could be proved if the destruction of the hypothalamus were found to alter significantly the Mecholyl reaction. Bilateral lesions of the posterior hypothalamus were produced. Note that, after complete coagulation, electrical stimulation (H) of this structure is much less effective on the blood pressure and the nictitating membranes. The effect of

Mecholyl on the blood pressure and the nictitating membranes is fundamentally altered. Therefore, the degree and duration of the hypotensive action of Mecholyl and the reflexly induced discharges of the sympatheticoadrenal system appear to depend on the hypothalamus.

Finally, Gellhorn feels that it is extremely doubtful that the vagus plays a significant role. The hypotensive action of Mecholyl is not significantly altered by vagotomy.

Funkenstein's findings[7, 10, 11] using the Mecholyl test patterns in psychotic and neurotic patients are of great interest. There was found to be no correlation between psychiatric diagnosis and C.S.R. pattern. The majority of his patterns showed either decreased or increased C.S.R. Electric convulsive therapy (E.C.T.) always led to increased C.S.R. and was predictably effective in those patients who began with low C.S.R. Patients with increased C.S.R. were made worse by E.C.T., yet did quite well with sedation (which leads to decreased C.S.R.) and other types of therapy. Of special importance was Funkenstein's observation that psychological and physiological improvement went hand in hand. In the dosage and time intervals used in this study, it would appear that reserpine, administered acutely, might prove beneficial in terms of central sympathetic responsivity in that it decreases C.S.R. in subjects who begin with increased C.S.R., and increases C.S.R. in subjects who initially have decreased C.S.R. If, indeed, physiological improvement correlates with psychological improvement as suggested by Funkenstein's observations, then it would appear desirable to extend the present study to patients receiving reserpine over prolonged periods to see whether or not such a correlation obtains.

Summary

(1) Ten subjects were studied with the Funkenstein test, using the blood pressure response pattern after injection of Mecholyl in order to estimate central sympathetic reactivity (C.S.R.) before and after the acute administration of reserpine and, later, of Amytal.

(2) Control studies showed three subjects to have normal C.S.R., three had increased C.S.R., and four had decreased C.S.R.

(3) The administration of 1.0 to 2.5 mg. reserpine led, 1 to 3 hours later, to a *decrease* in C.S.R. in those subjects who, in the control tests, showed normal or increased C.S.R., and an *increased* C.S.R. in those with decreased C.S.R. under control conditions.

(4) Of the eight subjects receiving Amytal, seven showed a *decrease* in C.S.R. and this was irrespective of their control C.S.R.

(5) Gellhorn's physiological studies of the effects of Mecholyl in cats appear to establish the validity of the Funkenstein test as a measure of central sympathetic reactivity in the intact organism.

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CLINICAL EFFECTIVENESS OF RESERPINE

By Frederic F. Flach

Department of Psychiatry, Cornell University Medical College; and The New York Hospital (Payne-Whitney Clinic), New York, N. Y.

Introduction

The purpose of this study is to investigate extensively the psychopathologic effects of reserpine in a small number of hospitalized psychiatric patients, in order to clarify specific indications and contraindications for its clinical use.

Method

The total number of patients in this series has been limited to 19. Diagnostically they may be grouped as follows: two acute schizophrenic reactions, six chronic schizophrenic reactions, one acute paranoid reaction, one manic excitement, and nine severe depressions. It was possible to obtain careful, continuous observations of the physiologic and psychopathologic changes occurring during the course of reserpine therapy. In addition to the recording of pulse, blood pressure, temperature, weight, and sleep, nursing charts included an uninterrupted 24-hour description of behavioral changes. These records, combined with the observations made by the individual psychotherapists and regular evaluations done by those responsible for this research project, constitute the material from which our findings have been drawn.

With the exception of two patients begun on low oral doses of reserpine, the following routine of administration was followed. Initially, 5 mgm. of reserpine was given intramuscularly twice on the first day of treatment. The dosage was then increased by 5 mgm. per day until a definite physiologic and/or psychopathologic response was seen, or until a maximum of 15 mgm. intramuscularly, twice a day, was reached. At this point, the patient was transferred to oral medication equal in amount to the maximum intramuscular dose. This was subsequently increased or reduced until a desirable level of control was reached, when the maintenance dose was established and continued for an indefinite period of time.

While under the influence of reserpine, the patients participated in all routine activities, except when extreme retardation necessitated isolation and bed rest.

Effective Day Dosage and Duration of Treatment

In those patients who responded well to reserpine, well-defined, beneficial effects were usually apparent within 3 to 8 days. Improvement was often rapidly evident within 24 hours, once the initially large doses of reserpine were reduced to a low maintenance level of about 6 mgm. per day. When the overall clinical effect was only "fair," beneficial changes occurred more slowly and gradually, over a period of 1 to 3 weeks. When improvement did not occur until after termination of reserpine, the effect was noted within 1 to 5 days following the last day of treatment.

The dosage range was quite variable because of the marked differences in

TABLE 1

RESULTS OF RESERPINE TREATMENT BY DIAGNOSTIC GROUPING

No.	Diagnosis	Good	Fair	Poor	Poor with post treatment improvement
8	*Schizophrenic reactions:*	*3*	*2*	*2*	*1*
	Acute				
1	Paranoid panic	1			
1	Catatonic withdrawal	1			
	Chronic				
2	Simple	1	1		
1	Simple with psychopathic, hysterical features				1
1	Undifferentiated excitement		1		
1	Sexual excitement			1	
1	Sexual excitement, epileptic			1	
1	Acute paranoid reaction:				1
1	*Manic-depressive reaction:*	*1*			
1	Acute manic excitement	1			
9	*Depressions:*	*1*	*3*	*5*	
3	Agitated paranoid		2	1	
1	Agitated with rut formation		1		
1	Agitated with hysterical features			1	
2	Paranoid			2	
1	Paranoid with organic features			1	
1	Paranoid, arteriosclerotic, post three electroconvulsive treatments	1			
19	Total	5	5	7	2

psychopathologic and physiologic responsiveness to reserpine among this group of patients.

For purposes of this study, patients were continued on the medication for at least two weeks, in the absence of any undue complications.

Results

The results of treatment have been recorded in TABLE 1. In general, they may be divided as follows: 5 "good," 5 "fair," 7 "poor," and 2 "poor while receiving reserpine with marked clinical improvement after termination of the drug."

Specific psychopathologic effects. On the assumption that the essential psychophysiologic structures of the schizophrenic reactions and mood disorders are different, the specific psychopathologic changes with reserpine have been evaluated in terms of the general diagnostic groupings, as demonstrated in TABLE 2.

In the *schizophrenic* reactions, the effects seem to have been clearly successful where the leading features are tension, fear, and anxiety with somatic components such as palpitations, feelings of choking, shortness of breath, and insomnia. These feelings may be associated with retardation of speech, thinking disorder, paranoid projections and delusions, specific phobic experiences,

TABLE 2

THE EFFECT OF RESERPINE ON SPECIFIC PSYCHOPATHOLOGIC FEATURES BY DIAGNOSTIC GROUPING

Alleviated	Variable	Unchanged or aggravated
Schizophrenic reactions		
Tension	Overactivity	
Retardation of speech	Overtalkativeness	
Withdrawal		
Resistiveness		
Anger	Resentment	Eroticism
Fear		
Anxiety*		
Associative disorganization		
Paranoid delusions		
Depression		Elation
Acute paranoid reactions		
Overactivity	Tension	
Posturing		
Masturbation		
Anxiety*		Resentment
Hallucinations		
Paranoid delusions		
Elation		Depression
Manic-depressive acute manic reaction		
Tension		
Overactivity		
Anger		
Fear		
Anxiety*		
Eroticism		
Paranoid projection		
Elation		
Depression		
Depression		
Tension	Overactivity	
Compulsiveness	Withdrawal	
Retarded speech		
		Resentment
Fear		Depression
Anxiety*	Delusions	Hypochondriasis

* Particularly when associated with somatic manifestations, such as palpitations, retrosternal pressure, shortness of breath, *etc.*

withdrawal, and subsequent depression. Where fear was associated with marked tension and somatic anxiety, the effect was good. Where "fearful thoughts" were present without some somatic component, the effects were more variable and often poor. Where strong erotic factors or actual sexual excitement were present, the drug only perpetuated or aggravated this pathology among female patients. No male sexual excitements were available for study. If elation (often associated with sexual stirring) was present or replaced depression in therapy, the outcome was usually poor. In one case, fear and withdrawal were replaced by hysterical and erotic overactivity, which disappeared within four days after the termination of treatment, leaving the patient anxious, somewhat depressed, with looseness of associative thinking, but much improved. The effect of reserpine on resentment and overactivity in this group is quite variable.

One *acute paranoid reaction*, probably bordering on a state of intense panic, whose marked tension, fear, and anxiety were associated with inappropriate affect, elation, overactivity, masturbation, hallucinations, and paranoid delusions, responded to therapy with amelioration of this leading psychopathology, but with increased resentment and considerable depression, which disappeared following termination of reserpine, leaving him much improved.

Only one *acute manic reaction* has been treated with reserpine. Within 48 hours, a marked reduction in tension, overactivity and overtalkativeness, elation and underlying depression, anger, fear, anxiety with somatic components and paranoid projections occurred. This reduction was maintained during and after termination of treatment. When anxiety was stirred by aggressive psychotherapeutic measures, increasing the dosage of reserpine permitted continuation of good control.

In the *depressive* group, anxiety and tension were often reduced and, in several cases, the patients became somewhat less restless and more sociable, with relief of paranoid delusions, but the depressive mood itself remained unaltered. Resentment, which was marked in some patients, was rarely alleviated. Sometimes there was an increased hypochondriacal overconcern with utilization of somatic sensations created by the drug. In several instances, verbal expression of underlying psychopathologic features increased.

As with hypochondriacal overconcern, in all groups wherever hysterical features were prominent, these would often shift to a significant exaggeration of otherwise mild somatic complications of treatment, counteracting other beneficial effects which might have been derived.

Sleep, weight, and pulse. In nearly half the cases, sleep was well controlled while, in the remaining half, interrupted sleep was persistent or aggravated, requiring additional night-time sedation. The control of sleep corresponded generally to the general effectiveness of treatment. Weight increased in all but four cases, ranging from a gain of 0.3 to 2.0 kg. per week, averaging 0.8 kg. per week. Pulse decrease was more uniform among those who responded well, and was more often absent among those who responded poorly to reserpine.

Complications

Complications in the use of reserpine were frequent. Milder complications included lethargy, fatigue, subjective complaints of weakness, dizziness, and coldness. Infrequently these feelings were of severe intensity. The most prominent severe complication of the treatment was a Parkinsonlike syndrome, consisting of generalized, recurrent tremors, shuffling gait, bland and masklike faces, some slurring of speech, motor weakness and coordination disability and, often, excessive drooling of thick, stringy saliva. These effects were most often noted in the schizophrenic group and, although presumably related to a neurophysiologic action of reserpine, they closely resembled certain types of catatonic states. At times, these effects were severe enough to necessitate temporary isolation and bed rest in order to prevent a deleterious effect on the patients' social morale. Lowering the dose alleviated these complications within 24 to 48 hours. There was no correlation between the severity of these symptoms and the dosage, except in the individual patient.

Another frequent somatic complaint was mild, lower extremity "discomfort." This feeling was often associated with restlessness and pacing, alternating with periods of lying flat or elevating the lower extremities. Whether these two symptoms are related and reflect peripheral vascular changes with pooling of blood in the lower extremities, which the patients attempted to alleviate by frequent contraction and relaxation of leg muscles or leg elevation, or whether the restlessness is an independent finding, reflecting central nervous system stimulation by the drug, is still unclear. These symptoms were mild or moderate in severity, and contributed significantly to the subjective discomfort of the patients.

One instance of ankle and facial edema and one case of multiple raised skin lesions were noted. These were considered indications for terminating reserpine, and disappeared within 48 hours after the last dose.

Discussion

On the basis of this investigation, reserpine appears to have a definite, although limited, place in the treatment of psychiatric disorders. The degree of variability of response to the drug is considerable, complicating its administration. Where beneficial effects appear late in treatment, the efficacy of reserpine may become doubtful because of the introduction of numerous unrelated factors, such as environmental measures and psychotherapy.

Where tension, fear, and anxiety with somatic components are prominent, reserpine seems to provide definite relief, with subsequent alleviation of related psychopathologic features such as withdrawal, delusions, and thinking disorder. Its effect on motor activity is variable, and the drug itself produces a restlessness often severe enough to counteract the relief of psychopathologic agitation. With regard to mood, depression in schizophrenic reactions is often relieved as the underlying psychopathologic state clears. Reserpine, however, does not seem to affect elation, whether elation is present initially or replaces depression during the course of treatment. In contrast, the mood disorder in depressive reactions is usually unchanged and often depression is increased, counteracting other beneficial effects. Eroticism, particularly sexual excitement, in female schizophrenics seemed to be maintained or aggravated by the drug whereas, in the manic phase of a manic-depressive illness, all elements of the psychopathologic picture were relieved, including eroticism and mood lability. Special consideration must be given to the somatic sensations created by the medication, which may be used by hysterical or hypochondriacal patients in a manner negating other beneficial effects. A number of patients, particularly in the depressive group, who had previously been able to function well socially and in interviews, covering up known, serious psychopathology, seemed to verbalize these features more often while on the medication.

Improvement of disturbed sleep appeared to be secondary to the clinical relief of psychopathologic fear and anxiety. The drug produced an increase in appetite and weight, which was complicated in many instances by the dynamic meaning of food to certain patients, particularly in the schizophrenic group.

No serious complications have been noted that would threaten the physical well-being of the patient, with the possible exception of one instance of facial and ankle edema, probably on a renal basis, which cleared with termination of the drug. Symptoms of restlessness and Parkinsonlike motor and coordination dysfunction, however, did occur, often counterbalancing the beneficial effects of the drug and increasing, rather than alleviating, management problems. These are of psychophysiologic interest, inasmuch as they were clearly more marked among the schizophrenic group than other groups, regardless of the outcome of treatment.

The lowering of pulse, seen in the majority of cases, presents another therapeutic problem. If electroconvulsive therapy is indicated following reserpine treatment, as would be the case with severe depressions, the diminished resilience and low level of autonomic responsiveness probably increases the cardiac hazards of electroconvulsive therapy. A waiting period of one to three weeks may be necessary before electroconvulsive therapy can begin, causing a significant delay in the therapeutic regime.

In nine patients, the reduction of anxiety and associated psychopathologic features permitted intensive psychotherapeutic measures which might not have been otherwise possible. These measures included four chronic schizophrenic reactions, one acute schizophrenic panic, one acute catatonic reaction, one acute paranoid reaction, one manic excitement, and one severe depression. The level of anxiety produced by the discussion of sensitive material could be readily and clearly controlled by adjusting the dosage of reserpine in the acute panic reaction and the manic excitement. Spontaneity was not usually impaired and often increased. The absence of any memory difficulty, a frequent complication to electroconvulsive treatment, provided an additional advantage permitting uninterrupted therapy.

Summary

Reserpine was administered to 19 hospitalized psychiatric patients who suffered from schizophrenic reactions and various types of depression. The drug was most effective in decreasing or controlling tension, anxiety, and fear, particularly where somatic components were present. Delusional material related to these strong emotions, as well as dissociative processes subsided. Psychodynamic factors considerably influenced neurological and other side effects, especially those resembling Parkinsonism. Intensive psychotherapeutic measures were facilitated by the use of reserpine.

CLINICAL USE OF RESERPINE IN PSYCHIATRY: COMPARISON WITH CHLORPROMAZINE

By M. Bleuler and W. A. Stoll
Psychiatrische Universitatsklinik, Zurich, Switzerland

During the autumn of 1953, we began to use the alkaloid reserpine (Serpasil),[1,2] a drug derived from the Indian plant *Rauwolfia serpentina*, as one of our standard treatments at the University of Zurich Psychiatric Hospital Burghoelzli, Zurich, Switzerland. At that time, the reasons which prompted this action were the following: Indian patients who came to us reported treatments with *Rauwolfia* which they had undergone in their native land. Simultaneously, we became familiar with the first Indian publications[3] describing long-established uses in India of the "insanity herb," the name *Rauwolfia* had received there. At the same time, Swiss physicians[4] began to publish their first reports on the use of reserpine in cases of hypertension. These latter communications gave scattered accounts of side effects of treatments with reserpine, such as apathy and a heightened need for sleep.

At the same time, chlorpromazine (Largactil, Megaphene, Thorasine) had already been introduced in the hospital. Chlorpromazine had demonstrated, on the one hand, great success but, on the other, it had brought with it extreme side effects, including severe pain when administered by injection. It accordingly became necessary to search for medications which would possess chlorpromazine's advantages but not its disadvantages. Since then, we have treated approximately 170 patients with reserpine. One of our co-workers, Doctor Mielke,[5] has devoted his full time during the past year to this therapy.

We have clearly observed that basic similarities and differences exist in the clinical effects of chlorpromazine and reserpine. Such a likeness of the clinical significance of reserpine and chlorpromazine is surprising, if one considers how completely different their chemical structures are. Animal experiments had demonstrated that both drugs do not attack the nervous system identically and, on the basis of pharmacological investigations, it could not have been predicted that these medications would show a clinical similarity. Curiously enough, however, two new important drugs, discovered and made known under completely different circumstances, were introduced into psychiatry within the same year. The one, a *Rauwolfia* alkaloid derived from an old Indian folk's remedy, was produced chemically pure by pharmaceutical scientists and applied as a treatment for hypertension. The other, chlorpromazine, was employed by French doctors, along with other phenothiazines, as an aid in narcosis.

Our presentation will be more intelligible and useful if we do not isolate our experiences with reserpine, but compare them, from the very beginning, with what we know about chlorpromazine. Later we shall compare these experiences with those we have gained from insulin and electroshock therapies. We should like to refrain from reporting, in this paper, too many quantitative findings. Complete statistical studies of our work can be found in publications by Weber[6] and Mielke,[5] of our hospital.

Basic Characteristics which Chlorpromazine and Reserpine Have in Common in Psychiatry

(1) Both medications, given in adequate doses, *soothe and relax patients remarkably, to an extent formerly unknown to us*. During the first two or three days of treatment, patients sleep for greatly increased periods of time during both night and day. Generally, they can be wakened without difficulty and are able to take food and execute their own body functions. As a rule, this increased need for sleep is reduced after a few days. In its place arise significant changes in the patient's mood and behavior. The patient becomes more indifferent, less impulsive, quieter, and more relaxed than before. It can also be observed that the emotional significance of symptoms such as delusions, hallucinations, and all kinds of moodiness decreases. In general, these mental changes correspond with conditions found to be typical in cases of post prefrontal leucotomy.

This description, however, has limitations. It must be emphasized that the psychological effects of these medications are subject to quantitatively large individual variations. In fact, there are often patients who completely fail to respond, even when doses are greatly increased. Sleepiness and tiredness, on the other hand, can be so strong that attending to the patient is rendered difficult. Now and then, it has also been noted that, instead of the patient becoming more relaxed and quiet, the paradox arises that just an opposite reaction takes place. He can become temporarily restless instead of calm. It is seldom that patients remain in this state for lengthy periods of time. Once in a while, strange increases of body movements or merely subjective feelings of inner restlessness can be observed. Frequently, cravings and instinctive strivings are briefly increased rather than lessened; for example, the patient may begin to have a large appetite.

(2) Outside of the similarity of mental effects, chlorpromazine and reserpine also have in common manifestations after *overdosages*, which result in an *extrapyramidal syndrome*. This symptom complex sharply differentiates itself from phenomena that arise after the application of hitherto employed sedatives and somnifacients, the latter of which lead to narcosis. Frequently, the extrapyramidal syndrome is only slight. It is then characterized by trembling, a masklike face, stiff gait, and loss of associative movements. In severe cases, however, a classical Parkinson syndrome presents itself: typical posture; typical gait—including propulsion and retropulsion—rigidity; cogwheel phenomenon; typical tremors; less frequently, pill rolling; and, more often, ptyalinism, *etc*. It is evident that the neurological manifestations of these medicaments go back, by means of a selective effect, to the brain stem. One is naturally tempted to conclude from this inference that the psychological effects are also a brain-stem effect. Such a conclusion appears to be a justifiable conjecture, but it has not been proved.

(3) Another characteristic which both of these medications have in common is that, administered as a hospital treatment, they can immediately effect severe psychiatric conditions in the same way that sleep, insulin, and electroshock therapies do. At the same time, they are, in general, *much less dangerous*

than the older treatments. Mortality occurs very seldom in spite of the frequency of their use. Even when cases of death have been described, one could just as well attribute the causes of death to complications that arose independent of the therapy. As far as we currently know, the extrapyramidal syndrome caused by overdosages seems to be no real danger, since it vanishes rapidly after therapy is discontinued, thereby emphasizing the fact that the all too frequent and tragic results of the older therapies (for example, prolonged comas, pulmonary complications, amnestic mental syndromes and fractures) do not accompany treatments with these medications. This statement should not be taken to mean that chlorpromazine and reserpine therapies are completely free of danger. The most important hazards to be mentioned are damages to the liver, local symptoms by injection, possible orthostatic collapses, intestinal complications, and addiction. In this regard, however, the complicating effects of chlorpromazine and reserpine are clearly distinguishable, and we shall discuss them as differences between the two drugs (see below) rather than as similarities.

(4) *The method of administration* of treatments with chlorpromazine and reserpine is similar, although dosages are completely different. For a few days, the medication is administered in large doses by injection. Then oral applications are substituted for intramuscular, and the doses are lowered. The moment and pace for changing doses depends completely on the patient's state of health. We have found that an initial dose of 200 mg. chlorpromazine per day (4 times 50 mg.), administered intramuscularly, closely compares with 10 mg. reserpine per day (2 times 5 mg.), also administered intramuscularly. Smaller doses are frequently adequate, as well as overdoses; for example, we sometimes administer daily 3 times 5 mg. reserpine or 300 mg. chlorpromazine. Both treatments generally last from two to four weeks.

Differences in the Psychiatric Application of Chlorpromazine and Reserpine

(1) Chlorpromazine tends frequently to *euphorize* depressed patients slightly. In general, reserpine fails to achieve this effect during therapy, and this property may be a disadvantage. On the other hand, we have already observed single cases of chlorpromazine addiction. We hope this danger is less frequent with reserpine, which seems to be the case.

(2) After only a few intramuscular injections, chlorpromazine generally causes large *infiltrates*, which bring about severe pains. This discomfort is a torment to the patient. We find it inexplicable that many research workers with chlorpromazine have failed to allude to this complication. An attempt was made to lessen these pains by applying local anesthetics concurrently with the drug. Such efforts proved unrewarding. Reserpine infiltrates occur quite seldom and are less extensive and painful. We find this an advantage reserpine has over chlorpromazine.

(3) *Parkinson symptoms*, as complications of chlorpromazine therapy, appear only in a small number of those cases which tend to improve with psychiatric treatment. The opposite is true of reserpine. In the majority of cases which respond well to the latter treatment, we find, at least, light Parkinson symp-

toms. We believe it would not be right to view these manifestations as insignificant and thereby disregard their importance. These symptoms distress many patients. On our part, as well, such situations bring about feelings of uneasiness, since we know how often Parkinson's syndrome is incurable, in fact progressive; for example, after carbon monoxide or mercury poisoning. We have not as yet observed or heard of any cases in which permanent damages, in the sense of a Parkinson syndrome, have occurred as a result of this treatment. We do not intend, however, to expose our patients to the medication for extended periods of time in order to learn whether or not the syndrome also appears during prolonged treatment. We are of the opinion that one should be more cautious and attempt to avoid, if possible, the Parkinson syndrome. In this regard, animal experiments seem indicated for data regarding cerebral changes occurring after prolonged applications of toxic doses of chlorpromazine and reserpine.

(4) Function tests have frequently determined that chlorpromazine can produce slight *damages to the liver*. In a small percentage of cases, a mild icterus appears. We have not as yet found liver damages due to reserpine, but our experience is still too small to say with certainty that reserpine is less harmful to the liver than chlorpromazine. The prospects of validating such a statement, however, seem promising. On the other hand, mild *gastrointestinal* symptoms, such as diarrhea or vomiting, appear in a small number of cases treated with reserpine. These complications occur chiefly at the beginning of treatment. Gastrointestinal symptoms probably appear more often during treatments with reserpine than with chlorpromazine.

(5) One often finds an *oversensitivity to light* of the conjunctiva and skin during chlorpromazine therapy. These manifestations can be observed only rarely during reserpine treatment. Reserpine, on the other hand, generally brings about a vasodilatation of the conjunctiva during the first few days of treatment.

(6) Now and then, bad eczemas develop on the hands of nurses who handle chlorpromazine. We have not as yet observed anything similar with reserpine.

(7) Whereas both drugs have a slight tendency to produce orthostatic collapses, they affect the pulse rate differently. Chlorpromazine often leads to tachycardia; reserpine, generally, to bradycardia. Both medications affect circulation in such a manner that care and close nursing supervision must be maintained when the patient rises from bed and walks about. Temperature is generally a bit lowered or raised. Many patients complain, as regards both medications, of a certain dyspnea.

Psychiatric Indications for Chlorpromazine and Reserpine

Conditions of excitation, irritability, and restlessness, as well as stuporous states with inner tension, are all suitable for these treatments. Therapy is particularly indicated when these conditions are mixed with dangerous behavior, aggressive outbursts, suicidal tendencies, inclinations towards self-mutilation, prolonged periods of food abstention, *etc.* To be sure, causal treatments are preferable whenever possible. Psychotherapy also has priority over medical treatment, if favorable results can be obtained. Physical counter-indications, such as circulatory weaknesses, previous Parkinson's disease, and chlorpromazine liver disturbances are scrupulously to be taken into account.

Such indications are found in a wide variety of psychotic conditions, and prescription for treatment is completely independent of the special diagnosis. By far the most frequent indication for the use of these drugs in mental hospitals is with schizophrenic states of excitement and tension. Manic and depressive states found in manic-depressive psychosis, or on any other basis, are also a frequent indication. These treatments also bring about gratifying effects in cases of senile excitation. Many of Bonhoeffer's acute exogenic reaction types have already been successfully treated, especially delirium tremens. Splendid results are also reported in weaning addicts from morphium. Less frequent indications are in cases of psychogenic states of excitement, especially when these states occur in mental deficients. Single cases of chronic compulsive neurosis in states of heightened anxiety and excitation have also responded well to these treatments. In Switzerland, at this time, Doctors Walther Büel[7] and Brander[8] are investigating the efficacy of reserpine and chlorpromazine in cases of choreic disturbances and, above all, in Huntington's chorea. They have found that approximately one half of these patients respond particularly well to reserpine.

When Should Chlorpromazine Be Prescribed and When Reserpine?

We are of the opinion that this question should be decided on the basis of the patient's *individual reactions.* When patients respond to reserpine by developing a rapid Parkinson syndrome, we switch over to chlorpromazine and hope the patient can carry this drug without developing the same symptoms. If local reactions due to chlorpromazine become unbearable, it is often possible to continue treatment successfully with reserpine. Physical counter-indications also give clues for special indications. For example, chlorpromazine is not recommended in cases of liver damage. For internal reasons, reserpine should be employed for hypertension. From a purely psychiatric point of view, we have learned that, if a rapid euphorisation is important, as in a majority of acute depressed states, then chlorpromazine is preferred. On the other hand, if addiction is to be overcome during longer treatments, reserpine should be tried first.

Full regard for the patient's unique mental reactions to the drug is paramount. For reasons we cannot explain, one patient reacts better to chlorpromazine, while another responds more favorably to reserpine. It is fortunate that we have two medications that can be exchanged, the one for the other, according to individual toleration and efficacy.

To What Extent Do Chlorpromazine and Reserpine Replace the Older Insulin, Electroshock, and Sleep Therapies?

At the present time, we can say that, when patients need to be soothed and relaxed rapidly, especially as regards their socialization and general improvement, reserpine and chlorpromazine are as effective as the older treatments and less dangerous. Do these two drugs, however, have *prolonged success?*

Such a question can be answered only after we have re-evaluated our opinions about lasting improvements reported as a result of insulin, electroshock, and sleep therapies. In this paper, we shall have to limit our discussion of these views to cases of schizophrenia. Fifteen years ago, clinicians were of highly divided opinion regarding the nature of shock treatments. Some practitioners stated that shock therapies affected the causes of schizophrenia, and certain workers even asserted that all, or at least 90 per cent of the schizophrenic population could be completely cured if only the treatment were employed early enough. One of us, M. B.,[9] who has been administering insulin therapy since 1936, summarized, in 1940, his experiences and findings based on an extensive statistical analysis. M. B. came to the following conclusions:

(1) Permanence of improvement after shock therapies is hardly greater than after schizophrenic remissions without them.

(2) Cures effected by shock treatments will be achieved preferably in the case of schizophrenics who would be expected to improve without shock treatments on the basis of a wavelike-acute course, administered in the light of personal history prior to illness and family relationships. In fact, shock therapies seldom produce lasting cures in schizophrenics whose personal psychodynamics, chronic course, and family constellation would necessitate, from the very beginning, an unfavorable prognosis.

Since then, our experiences, in general, have substantiated these findings. Today we can no longer find grounds for believing shock therapies are causal treatments. Such treatments are merely therapies which subdue and improve the patient, and accelerate his cure. They facilitate human contact and, thereby, psychotherapeutic accessibility. As far as we know, their mode of effect travels over unspecific metabolic and mental crises which make patients helpless, lead to regression, and renew readiness for interpersonal relationships.

If we view the nature of shock treatments for schizophrenia in this light, our original question must be changed. The question is no longer whether chlorpromazine and reserpine are just as much causal treatments for schizophrenia as the older shock therapies. A more accurate question is: Are treatments with chlorpromazine and reserpine as effective as the older therapies in improving, socializing, and, in cases of curable schizophrenia, accelerating and creating readiness for contact and psychotherapy?

Our period of observation, since the introduction of these treatments, is much too short to answer this question on the basis of convincing statistical studies. It was many years before we could say, with any degree of certainty, whether or not the older shock therapies were truly efficient therapeutic weapons. Therefore, we are not about to begin having illusions about our first experiences with these new medications. We have not as yet definitely discovered what actual advances and disadvantages chlorpromazine and reserpine have over the older therapies.

We are proceeding, at present, on the basis of indefinite impressions. Until now, we have learned that treatments with chlorpromazine or reserpine achieve as much as the older therapies do in the most acute cases of schizophrenia, where a rapid tendency to cure is present. Included under such cases are, above all, schizophreniclike psychoses, for example, or as they are called by some clinicians, oneiroidal psychoses, motility psychoses, schizophrenic reactions, *etc.* In *conditions of chronic and severe schizophrenia* the new drugs can improve, tone down, and socialize patients as well as the older treatments do. All of these therapies, however, rarely cure such patients.

There remains, on the other hand, a group of *acute or subacute schizophrenics* who are curable, but whose cure demands much time and often takes many months. In these patients, chlorpromazine and reserpine have produced rapid temporary improvements but, in many cases, relapses have occurred. It seems to us that insulin therapy produces better results in such cases than do the new medications. Insulin therapy also seems to bring about a more lasting and basic psychotherapeutic accessibility than the newer treatments.

Such guiding principles are valid, however, only for the majority of cases. Individual instances can contradict these observations. In all forms of schizophrenia, we experience the fact that patients, for unexplainable reasons, can respond better or worse to one treatment than to another.

Summary

(1) Reserpine and chlorpromazine treatments produce similar effects in severe psychiatric hospital patients. They relax and soothe patients, make them better-balanced, and allow them to recover from ill health. Reserpine and chlorpromazine are as efficient and less dangerous than extended narcosis, insulin, or electroshock therapies.

(2) Advantages that reserpine has over chlorpromazine are that it causes less painful infiltrates after intramuscular injections, and that it probably causes less damage to the liver. Chlorpromazine, on the other hand, has the advantage that it less frequently leads to Parkinson symptoms.

(3) There are areas in the treatment of schizophrenia in which both reserpine and chlorpromazine can achieve, with less danger, the same results as the older physical treatments: in the treatment of preacute, short-lasting schizophrenic or schizophreniclike psychosis, for example, and in treating severe chronic schizophrenics. Curable schizophrenics having a slow tendency to cure, however, appear, on the average, to react more favorably to insulin therapy than to chlorpromazine or reserpine.

(4) Reserpine and chlorpromazine are also indicated in cases of manic-depressive psychosis, in organic and psychogenic states of excitation and, probably, in choreic cases as well.

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CHLORPROMAZINE AND RESERPINE IN THE TREATMENT OF PSYCHOSES

By Vernon Kinross-Wright*
Baylor University College of Medicine, Houston, Texas

Throughout its long and checkered history, psychiatry has witnessed many novel and sometimes quite disreputable therapeutic endeavors. Some of these attempts have flowered briefly in the warmth of human hopes, only to wither away under the harsh glare of public scrutiny. Few have survived more than a decade or two. Even so, these more ancient remedies have been incorporated, from time to time, into our modern methodology. We learn, for example, in a recent issue of *The American Journal of Psychiatry*[1] that convulsive treatment was in vogue about 200 years ago. Reserpine is such a treatment. Known and utilized in the management of mental disorders in its native form for many centuries, it has now come of age. Its cousin chlorpromazine, a synthetic drug made in France a few years ago, is but an infant by comparison. Both of them are now creating much interest among psychiatrists. Science rarely progresses in an even and predictable fashion, but rather by leaps and bounds. In the intervening period there is a tendency toward stagnation, with over-elaboration and attenuation of existing knowledge and practice. The innumerable variations on the themes of electroconvulsive therapy, barbiturate compounds, and psychoanalysis exemplify this principle. The discovery of chlorpromazine or reserpine alone would have been encouraging. Their arrival together—and no doubt they are merely the beginning—must surely indicate the passing of another milestone.

Already both drugs are in widespread use throughout medicine despite the facts that adequate criteria for treatment are lacking, that authoritative reports (in the United States) are scarce, and that the dangers are not fully explored. Surely use of the drugs has become extensive because they are generally safe, almost universally effective to some degree, easy to administer, and do not ordinarily impair consciousness. Moreover, their mode of administration does not offend the sensibilities of even the most tenderhearted.

Case Material and Methods

This paper concerns the author's experiences with these two drugs in the treatment of schizophrenia and affective disorders. All the patients were psychotic, and all were treated on the psychiatric service of a teaching hospital by the author personally. Sex distribution of the patients was approximately equal. About two thirds of the patients were white. Ages ranged from 13 to 81. The patients included in this paper were unselected, since all patients admitted to the hospital in the schizophrenic or affective categories have been treated with one or both of the two drugs. There have been a few exceptions because of shortage of drug supplies in the early stages, previous quick response to some other therapy, and conflict with other projects. Patients who received other treatment concurrently with chlorpromazine or reserpine have been excluded.

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* The author is indebted to Doctor Jock L. Graeme of Ciba Pharmaceutical Products, Inc., Summit, N. J., for supplying reserpine (Serpasil) and to Michael Buckly of Smith, Kline and French, Ltd., Philadelphia, Pa., for supplying chlorpromazine (Thorazine).

The methodology of treatment has been dictated very largely by the necessity for rapid turnover of patients in a city hospital in an area with a great shortage of psychiatric beds and limited facilities for long-term treatment of any kind.

Initial experiences with chlorpromazine confirmed European reports[2, 3] of its efficacy in allaying excitement and obviating the need for restraint of disturbed patients. Even with doses of 200 to 400 milligrams daily, however, some of the patients showed more significant benefits in so far as thinking and mood were concerned. These observations led to the utilization of greater and greater doses of chlorpromazine up to a present maximum of 4000 milligrams daily. With these massive doses, remarkable changes occurred in the disease picture. Not only were symptoms controlled, but the thinking process became logical and realistic. Affect took on a normal quality. The patients were able to return home to resume their lives where they left off when sickness overtook them. In some instances, they did better than ever before.

Because of known side effects of chlorpromazine administration and others which might be expected to occur with such large doses, daily increments of the drug were small. Since fears of dangerous complications proved unfounded, treatment was accelerated. Once again it became apparent that both rate and amount of dosage were positively correlated with clinical outcome.

These considerations have led to the adoption of the following intensive chlorpromazine treatment schedule at the present time:

On the first day the patient receives 200 or 400 mg. Chlorpromazine is usually given in four divided doses in the 24 hours. In the absence of knowledge about the absorption, excretion, and blood levels (currently being investigated), this dosage is most convenient. Rapidity of action and greater sedation are achieved by intramuscular administration during the first few days. In a majority of psychotic patients, such administration is necessarily mandatory. Each day thereafter, the amount of drug is increased by 400 mg. As soon as the patient manifests signs of improvement, besides those attributable to sedation and improved appetite, treatment leaves the first stage or "period of initiation." The signs looked for are increase of communication, social responsiveness, and increased depth of affect. In the second or "therapeutic" stage, which lasts from 5 to 10 days, the maximum dosage is maintained while improvement continues. Improvement is usually rapid during this period and is very noticeable from day to day. When the rate of improvement begins to lag, the third stage begins, even though some evidences of psychosis may still be present. In this latter stage, the daily amount of chlorpromazine is decreased by 400 mg. each day. The patient is discharged from hospital when he has reached a level of 200 to 400 mg. a day. He may require this maintenance dose for a few weeks or many months. While this treatment schedule is fairly standardized, each patient still requires individual attention for best results.

Reserpine was not used by the author until the middle of 1954. Preliminary trials with both intramuscular and oral preparations were disappointing in the suggested doses of 5 to 10 mg. daily. It has since been recognized that this was probably the result of too brief treatment. As reserpine and chlorpromazine had many effects in common, an attempt was made to duplicate the successful chlorpromazine intensive treatment schedule. Starting with a dose of 5 mg. daily, either by the parenteral or oral route, an additional 5 mg. was added each day, up to a total of 60 mg. While all patients were more relaxed and slept better initially, there was no obvious change in their pathological thoughts or feelings. As the dose rose above 30 mg. daily, signs of Parkinsonism, confusion, and profound inertia became apparent. Two patients on 60 mg. remained in this condition for several weeks after the drug was withdrawn. With a few exceptions, none of the patients in this group benefited appreciably. The adoption of a third method led to better results. Patients are now given 5 mg. intramuscularly in the mornings only. Concurrently, they receive oral medication starting with 1 mg. twice daily, which is slowly increased, in 1-mg. steps, to a maximum of 10 mg. By the end of the third week, parenteral administration is discontinued, but the same oral dosage is maintained. Improvement is usually not discernible until the third week and is gradual but, as with chlorpromazine, patients have shown striking reversals of psychotic disturbance. Experience with reserpine has not been sufficiently extensive to predicate the necessity for prolonged medication after the patient has been sent home.

Gradation of Results

Remission implies disappearance of subjective and objective evidence of mental disease, with resumption of normal life. *Much improved* refers to patients who are able to live at home and even work, but still have residual symptoms. *Improved* signifies those patients who were relieved of some major symptoms, but whose basic illness persisted in modified form. *Unchanged or worse* is the final and self-explanatory category.

Results

A detailed consideration of the results will not be made in this paper. It may be found elsewhere.[4, 5] TABLES 1 and 2 summarize the response of 121* schizophrenics to chlorpromazine or reserpine. TABLES 3 and 4 refer to patients with one or another phase of the manic-depressive psychosis. A few cases of reactive depression of great severity are also included. Patients treated with a combination of the two drugs are covered in TABLE 5. It should be noted that these 23 patients also fall into one of the other tables, since they had all previously received reserpine or chlorpromazine alone.

It is noteworthy that 72 per cent of the schizophrenics treated with chlorpromazine fall into the first two categories of improvement. All returned home after an average stay in hospital of slightly over one month. Some of the patients in the third category were able to return home with or without combined reserpine and chlorpromazine treatment later (the cause of the

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* Three patients received both drugs at different times.

TABLE 1

SCHIZOPHRENIA TREATED WITH CHLORPROMAZINE

Diagnosis	Number of patients	Remission	Therapeutic response		
			Much improved	Improved	Unchanged or worse
Catatonic	11	6	4	1	
Hebephrenic	12	4	5	2	1
Simple	1				1
Paranoid	47	17	17	10	3*
Undifferentiated	13	2	5	4	2
Mixed	13	5	5	3	
Total	97	34	36	20	7

* 1 died.

TABLE 2

SCHIZOPHRENIA TREATED WITH RESPERINE

Diagnosis	Number of patients	Remission	Therapeutic response		
			Much improved	Improved	Unchanged or worse
Catatonic	4		1	2	1
Hebephrenic	5	1	1	1	2
Paranoid	9		3	4	2
Undifferentiated	4			3	1
Mixed	5	1	1	1	2
Total	27	2	6	11	8

TABLE 3

AFFECTIVE DISORDERS TREATED WITH CHLORPROMAZINE

Diagnosis	Number of patients	Remission	Therapeutic response		
			Much improved	Improved	Unchanged or worse
Endogenous and symptomatic depression	23	7	6	6*	4
Reactive depression	4		2	1	1
Mania	11	7	2	1	1
Total	38	14	10	8	6

* 1 died later.

single death is still under investigation). Reserpine, generally, failed to produce the same degree of improvement as chlorpromazine. It must be remembered, however, that a number of these patients must be regarded as inadequately treated because of previously mentioned difficulties in determining the optimal dosage.

TABLE 4

AFFECTIVE DISORDERS TREATED WITH RESERPINE

Diagnosis	Number of patients	Remission	Therapeutic response		
			Much improved	Improved	Unchanged or worse
Endogenous and symptomatic depression	5			2	3
Reactive depression	2			1	1
Mania	3		2	1	
Total	10		2	4	4

TABLE 5

CASES TREATED WITH CHLORPROMAZINE AND RESERPINE IN COMBINATION

All cases previously given either or both drugs alone without substantial improvement

Diagnosis	Number of patients	Number previously treated with chlorpromazine	Number previously treated with reserpine	Remission	Much improved	Improved	Unchanged or worse
Schizophrenia (all types)	14	10	8	3	4	4	3
Depression (all types)	6	6	1			1	5
Mania	3	2	1	2		1	

Disturbances of mood, in general, were not so favorably influenced by either drug. Fifteen of the depressions, however, were relieved, completely or to a great extent, by chlorpromazine. It was felt that many of these would have responded equally well and rather more quickly to electroshock treatment. Most of the patients who failed to improve significantly did well later with electric shock. In conformation with the findings of others,[2, 6] manic patients responded dramatically to chlorpromazine. Two patients were resistant, however, and one became much worse on the drug. Both of these patients were later treated with a reserpine-chlorpromazine combination and recovered. Depressed patients showed almost no good response to reserpine, and half of them were made worse. Two of three manic patients showed a very satisfactory improvement, though more slowly than with chlorpromazine.

Combined reserpine-chlorpromazine therapy was used only in intractable cases. In view of this fact, it is considered that the results were extremely favorable. It was not necessary to give extremely large doses of either drug to produce rather prompt response. Unfortunately, side effects were frequent even with the lower doses.

Side Effects

Chlorpromazine administration is attended by more side effects than reserpine. The author has discussed them in detail elsewhere.[7] It is convenient to consider these effects in five groups. The first group includes those due to local irritation of the mucous membranes occurring in a small percentage of patients. The second group of effects, such as dryness of mouth, miosis, nasal congestion, constipation, hypotension, and tachycardia occurs in a majority of patients. Disturbances of temperature regulation, increase of appetite, somnolence, menstrual disturbances, and inhibition of drive with a generalized feeling of weakness have been ascribed to interference with central regulatory mechanisms. These effects were frequently related to the size of dosage. Obstructive jaundice, dermatitis, and photosensitization were regarded as sensitivity reactions. Characteristically, they did not recur with a second course of treatment. The last group of side effects include Parkinsonism, confusion, seizures, tremor without rigidity, and lactation in the absence of pregnancy. The first three groups of side effects were not a source of great concern. They were most noticeable in the first days of treatment and usually diminished in spite of increasing amounts of drug. Dermatitis was severe enough to necessitate withdrawal of drug in two patients. The one case of jaundice was mild and cleared in a few days. Studies on patients outside this series indicate that it is of the obstructive type and resembles that caused by methyltestosterone.[8]

The side effects of reserpine fell into groups 2, 3, and 5. There were no local irritant effects. Hypotension, bradycardia, dry mouth, nasal congestion, and miosis were often conspicuous. They were more persistent than with chlorpromazine but appeared more slowly and were correspondingly less annoying to the patient. Increase of appetite, sleepiness, and inertia were very striking accompaniments of reserpine therapy. Changes in temperature regulation were not found. Parkinsonism, tremor without rigidity, seizures, confusion, and paresthesiae were noted.

When reserpine was given intensively in doses up to 60 mg. daily, all patients developed muscular rigidity of the cogwheel type, weakness, salivation, difficulty in swallowing and talking and, sometimes, a coarse tremor. This condition persisted for as long as one month after drug withdrawal. With a less intensive reserpine regime, this clinical picture occurred in about 15 per cent of the patients. The Parkinsonism of chlorpromazine is similar, though usually it resembled the naturally occurring Parkinsonism more faithfully. Pill-rolling tremor was visible, and there seemed to be less inertia and apathy. This condition also occurred in about 15 per cent of the patients. The origin of this profoundly interesting reaction is still a matter of speculation. Recently Doctor John Perry and the author have succeeded in reproducing it in primates. While Parkinsonism is undoubtedly a sign of toxicity, it has always been reversible and, unless too severe, is not an indication for discontinuance of medication.

The development of a confusional state in a few patients treated with large doses of both drugs is a clear sign of overdosage. The drug should be withdrawn immediately and the delirium will fade rapidly.

Two patients on reserpine and one on chlorpromazine experienced brief *grand-mal* seizures. There had been no history of convulsive disorder. The electroencephalogram was normal in the one case studied. There is evidence, however, that chlorpromazine has anticonvulsant activity in some cases.[5, 9]

Paresthesiae and fleeting muscular sensations were described by a number of subjects on reserpine but not on chlorpromazine. Lactation and menstrual disturbances were limited to chlorpromazine.

Two further effects require mention, since, potentially, they could be dangerous. Chlorpromazine, but not reserpine, enhances the action of other drugs, especially opiates. Chlorpromazine and, to a lesser extent, reserpine have modified the clinical picture of intercurrent physical illness. Fever and leukocytosis have been minimal in several cases. One patient complained so little of pain that a surgical abdomen was almost overlooked. It has been the author's practice to reduce or withdraw medication if signs of physical illness presented themselves.

Discussion

Most of the published work[1-10] and many unpublished observations[11] on the use of these two drugs point to their efficacy in many kinds of neuropsychiatric states. There is, however, no agreement about the best way of administration. The reasons for the dosage schedules used by the author have already been given. These reasons apply, of course, only to schizophrenia and affective disorders. Excellent therapeutic results have been obtained in delirium, neuroses, and behavioral disorders of children with much smaller amounts of chlorpromazine and reserpine. Schizophrenia responds better to chlorpromazine than to any other treatment the author has used. The improvement rate is high, and the quality of improvement excellent. It would be premature, after one year's study, to speak of cure, even though cure appears to be a possibility at the present. It is essential that treatment be adequate and rapid. The average therapeutic dose is about 2000 mg. daily. Where relapse has occurred or seemed imminent because of inadequate dosage, a second course of treatment should be given. With few exceptions, the subjects of this study have been followed in the outpatient clinic for adjustment of the maintenance dose, which varies for each individual. Some schizophrenics require indefinite administration. One paranoid schizophrenic relapses within two or three days if she stops medication. With it, she has remained symptom-free for over one year. A majority of the patients are able to discard chlorpromazine after three to four months, however. In keeping with the episodic nature of their illness, manic and depressive patients are usually able to do without the drug after a few weeks. The value of small doses of chlorpromazine for preventing further attacks is under study. It appears likely that the same considerations will apply to reserpine, but experience is too limited to be certain.

Duration of illness is a significant variable in the evaluation of any treatment. TABLE 6 shows the results achieved with schizophrenics, taking this variability into consideration. It can be seen that success does diminish with chronicity, as it does with other therapies. Patients who have been sick for eight years or more, however, have made remissions, especially in the paranoid group. It is further possible that more energetic treatment would have brought better results. Reserpine and chlorpromazine in combination have proved useful in chronic cases.

The results also reflect the symptom picture exhibited by the patient. Of the schizophrenics, the paranoid type does best. A detailed analysis will be

TABLE 6

RELATIONSHIP OF DURATION OF ILLNESS WITH IMPROVEMENT IN SCHIZOPHRENIA TREATED WITH CHLORPROMAZINE AND RESERPINE

Duration	Treatment	Number of patients	Remission	Much improved	Improved	Unchanged or worse
Less than six months	Chlorpromazine	30	15	11	3	1
	Reserpine	11	1	4	3	3
	Both	6	1	1	2	2
Between six months and two years	Chlorpromazine	28	9	13	6	
	Reserpine	5	1	1	3	
	Both	5		2	2	1
Over two years	Chlorpromazine	39	10	12	11	6
	Reserpine	11		1	5	5
	Both	3	2	1		

presented elsewhere.[12] Mania responds in all cases to the one drug or to the other. Endogenous depression is influenced favorably in many cases, while reactive depression is only rarely so influenced. Reserpine, however, proved disappointing in the treatment of depression.

This paper is not primarily concerned with combinations of chlorpromazine or reserpine with other forms of treatment, but several facts are worth mentioning. They have been used with electroshock treatment very effectively, and they permit the use of less shocks than would normally be required. In addition, postshock confusion is lessened. Two schizophrenics in this series had had no less than two lobotomies in the course of very chronic illnesses without substantial benefit. One has been in remission for six months following chlorpromazine, and the other is working for the first time in nine years after receiving chlorpromazine and reserpine together, though still psychotic. The increased accessibility of almost all patients taking the drugs, of course, places them in a better position to receive psychotherapeutic help. Some help in readjusting to difficult personal and home situations is usually necessary with any hospitalized patient. It has been surprising how the improved patients have been able to settle down at home and secure jobs with only minimal help. None of the patients in this series has been given systematic psychotherapy.

Even in cases where ultimate therapeutic results are meager, the unique properties of the two drugs in producing sedation without confusion, reducing drive without coma, and in stimulating appetite are valuable. They have changed the atmosphere of every disturbed ward where they have been used, and also the outlook of the personnel who work there. Where rapid sedation is required, chlorpromazine is the better drug. Even oral administration produces effects within 30 minutes. Reserpine, given orally, takes 24 hours or longer before appreciable effects are secured.

The disadvantages of the compounds are not great. Some side effects, in particular the sensitivity reactions to chlorpromazine, are unavoidable but are rarely severe. Parkinsonism convulsions and confusional states are matters for careful management, but not for alarm.

Summary

The use of chlorpromazine and reserpine in schizophrenia and the affective disorders has been described. For best results, chlorpromazine should be given intensively and in large doses. The opposite is true for reserpine, which should be given in small doses over a longer period of time. Both drugs bring about remissions in schizophrenia, though chlorpromazine appears to be more effective. Mania responds well to either drug. Depressions, particularly the reactive type, do not respond so well to chlorpromazine and may be aggravated by reserpine. Combinations of the two drugs have been valuable in obstinate cases. The two drugs share a number of side effects, but chlorpromazine alone causes sensitivity reactions.

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A PRELIMINARY REPORT ON THE TRANQUILIZING EFFECT OF RESERPINE*

By Robert R. Luttrell and Andrew V. Morrison
4167th United States Air Force Hospital, Travis Air Force Base, Calif.

Following the recent publications of optimistic first reports on the tranquilizing effect of reserpine, the office of the Surgeon General, United States Air Force, initiated research into its application for neuropsychiatric patients. The Air Force has the mission of flying many psychotic patients from outlying posts to treatment centers in the United States. Sedation of these patients is a major problem, for severely disturbed psychotics may become a threat through their violent behavior during flight. In the air, it has been found necessary to reverse the current trend toward minimal use of restraints and sedation in the air. Standard operating procedure calls for restraining cuffs on the patients' hands and feet, and for strapping them securely to a litter. In addition, they are usually given up to 7.5 grains of Sodium Amytal, so that the patient spends most of the flight asleep. The magnitude of this transportation problem can be seen in considering that 20 per cent of the patients that are evacuated by air are psychiatric casualties. At Travis Air Force Base, in California, about 2000 closed ward psychiatric cases arrive annually from the Pacific area. They are then flown from Travis to military hospitals near their homes. This mission could be more easily accomplished if a nonsoporific sedative were available. With such sedation, a patient could help care for his bodily needs as well as be more alert should a rare exigency arise.

Research was undertaken to determine whether or not reserpine could be used either to replace Sodium Amytal or to act as an adjunct to it for our special air evacuation needs.

This preliminary report is based on the study of 100 neuropsychiatric air-evacuation patients requiring closed-ward care. No selection process was used. Patients who remained for sufficient time were studied. These patients were mostly schizophrenics, but they include other psychiatric categories. They had been evaluated in detail overseas. In general, these patients had been hospitalized no longer than three months before a decision was made for their evacuation to United States treatment centers. Upon arrival at Travis Air Force Base, the authors made a detailed mental status examination on each patient. Then intramuscular injections of reserpine were administered. Dosage levels were 10 mg., 5 mg., and 2.5 mg. Careful efforts were made to avoid any suggestions to the patient as to the effects of the drug. During the succeeding 24-hour period, we re-examined the patients, and the psychological and physiological changes were recorded.

TABLE 1 shows the number of patients in each diagnostic category. As can be seen, the greatest number of patients were paranoid schizophrenics. The next largest group was schizophrenics, NEC, which means "not elsewhere classified" or "unclassified" because they do not fit easily into the four classical

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* The reserpine (Serpasil) used in these experiments was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE 1
DIAGNOSES OF PATIENTS STUDIED

	Acute	Chronic	Total
Psychoses			
Schizophrenics			
Paranoid	22	10	32
NEC	25	5	30
Catatonic	10	1	11
Hebephrenic	—	—	1
Latent	—	—	2
Manic-depressive, manic			4
Psychotic depressive reaction			1
Organic brain syndrome			4
Neuroses			
Anxiety reaction			1
Depressive reaction			3
Character disorders			
Inadequate			4
Schizoid			2
Cyclothymic			1
Emotional instability			2
Mental deficiency			2
			100

types. The table shows the number in other psychotic groups. There were only a few nonpsychotic patients in our study, since such patients rarely need closed-ward care.

As the purpose of our research was to determine the sedative effects of reserpine, we focused our attention mainly on the excitability of the patient rather than on his diagnostic category. In order to compare various patients described by previous examiners as disturbed, combative, hyperactive, *etc.*, we constructed a rating scale of manifest biological activity. We found this scale more precise than descriptive words in rating patients according to their excitability.

TABLE 2 gives some characteristics of the six steps in this scale. We classified the state of manic delirium, catatonic excitement, and paranoid rage at the one extreme of the scale. We called this greatest degree of biological activity level 5. The next most active group, level 4, consisted of driven,

TABLE 2
LEVELS OF BIOLOGICAL ACTIVITY

Level	Characteristics
5	Manic delirium, catatonic excitement
4	Driven, hypomanic, garrulous
3	Zestful, energetic, active
2	Calm, placid, leisurely
1	Dull, lethargic phlegmatic
0	Inert, stuporous, waxy flexibility

Table 3

Biological Activity Levels of Patients

	0	1	2	3	4	5
Psychoses						
Schizophrenics						
Paranoid		1	14	11	5	1
NEC		2	11	12	4	1
Catatonic	1	4	3	2	1	
Hebephrenic			1			
Latent			2			
Manic-depressive, manic			1		2	1
Psychotic depression			1			
Organic brain syndrome				3	1	
Neuroses						
Anxiety reaction			1			
Depressive reaction		2	1			
Character disorders						
Inadequate		1	1	2		
Schizoid			1		1	
Cyclothymic			1			
Emotional instability			1	1		
Mental deficiency		1			1	

hypomanic, or garrulous patients. Groups 4 and 5 were considered pathologically hyperactive. Entering the average range of activity, we found the zestful, energetic, and active individuals, classified at level 3. Still in the average range are the calm, placid, leisurely persons, at level 2. Proceeding to the pathological hypoactive range, those dull and lethargic patients were rated at level 1, while inert and stuporous patients were rated at level 0.

This scale could be conceived as a rating for severe, moderate, mild hyperactivity and mild, moderate, and severe hypoactivity. Activity here is considered as an individual's observed way of discharging energy on an enduring level during his illness. We found the scale applicable to all patients in our study regardless of diagnosis. Rating the level of excitability of our patients seemed mandatory prior to giving a sedative drug.

Using the rating scale, the patients were reclassified, as is shown on Table 3. It will be noted that, in each diagnostic category, the patients vary considerably from hypoactivity to hyperactivity. Most of the patients studied, including paranoid and catatonic schizophrenics, fell in the average level of activity. In short, most of our patients were characteristically sedate before the administration of reserpine.

Following the initial mental examination and rating of biological activity, reserpine was administered.

The results of our second examination, showing reserpine sedation in the diagnostic categories, are shown in table 4. We judged a patient sedated if his activity rating decreased. Paranoid schizophrenics, schizophrenics, NEC, and manic-depressive psychosis, manic type, were the diagnoses most successfully sedated. We do not include the nonpsychotic patients, since their total number was not high. It should be noted that most of the patients were not sedated by reserpine. One might mistakenly conclude that reserpine has little

TABLE 4

RESERPINE SEDATION IN THE DIAGNOSTIC CATEGORIES

	N	% Sedated	% Not sedated
Psychoses			
Schizophrenics			
Paranoid	32	19	81
NEC	30	23	77
Catatonic	11	9	91
Hebephrenic	1	0	100
Latent	2	0	100
Manic-depressive, manic	4	75	25
Psychotic depression	1	0	100
Organic brain syndrome	4	25	70
Neuroses			
Anxiety reaction	1	0	100
Depressive reaction	3	0	100
Character disorders			
Inadequate	4	0	100
Schizoid	2	50	50
Cyclothymic	1	0	100
Emotional instability	2	0	100
Mental deficiency	2	50	50

TABLE 5

RESERPINE SEDATION AND LEVEL OF BIOLOGICAL ACTIVITY

Level	N	% Sedated	% Not sedated
5	3	100	0
4	15	73	27
3	31	16	84
2	39	3	97
1	11	0	100
0	1	—	—

TABLE 6

PHYSIOLOGICAL SIDE EFFECTS

Amount reserpine	N	Percentages			
		Severe	Moderate	Mild	None
mg.					
10	27	40	22	19	19
5	24	13	34	28	25
2.5	49	10	36	35	19

sedative effect with all psychotics. This relatively large percentage of patients not sedated resulted because the drug did not further calm the already sedate patients. This consideration of activity levels is intriguing, so let us recast our results according to biological activity.

TABLE 5 shows that 100 per cent of our most excited patients were sedated.

The driven, hypomanic, or garrulous patient we called level 4 were sedated in 73 per cent of the cases. Entering the average range of biological activity, we note, as before, that no further sedation is observed in the majority of patients. Pathologically hypoactive patients were also not sedated. Hence we find in our study that the majority of patients sedated appeared in the pathologically hyperactive levels. It would seem, from these observations, that the sedative action of reserpine is a function of the enduring biological activity level of the patient rather than the psychiatric diagnostic category. The effect on the excited patients was calming, with a decrease in combativeness, motor behavior, and tension levels. Occasional patients who characteristically were lethargic and dull were not controlled by reserpine, and they sporadically demonstrated impulsive, aggressive outbursts.

Also of importance in considering the transportation of psychiatric patients is the frequency of undesirable physiological side effects.

Table 6 shows the percentage of patients who experienced various degrees of side effects. A typical severe reaction included throbbing headache, marked flushing of the face and conjunctiva, frequent nausea, vomiting and diarrhea, and marked general malaise usually described as "I feel like I'm getting the flu." These symptoms usually started within two hours after drug administration and kept the patient bedridden from six to eight hours. When we used 10 mg. of reserpine, 40 per cent of our patients became ill and showed this severe symptomatology. As the drug level dropped, the incidence of severe reactions decreased. A moderate response consisted of headache, less severe flushing of the face and conjunctiva, occasional nausea, vomiting and diarrhea, and moderate malaise. A mild reaction was judged present when the patient had minor transient complaints of discomfort. At the lowest dosage used in this study, 46 per cent of the patients experienced severe or moderate side effects and were considered poorly prepared for transportation by air.

We conclude from our observations that:

1. Psychiatric patients in a continual state of hyperactivity will be sedated in the majority of cases by reserpine. The prediction of sedative effect seems a function of biological activity rather than psychiatric diagnosis.
2. Toxic effects seem more common than desired, leaving the patient less ready for flight. Further research seems indicated, so that side effects may be lessened.
3. Because of its lack of universal sedative action and undesired side effects, reserpine at present cannot be considered a satisfactory substitute for Sodium Amytal in the transportation by air of psychiatric patients. As an adjunct to Sodium Amytal, reserpine is of use in sedating markedly hyperactive patients prior to flight.

These observations suggest that, since reserpine sedates pathologically hyperactive people, regardless of psychiatric diagnosis, it may be useful in treating excitements from combat reactions, civilian emergencies, and atomic disasters.

THE USE OF RESERPINE IN IRRITABLE AND HYPERTONIC INFANTS

By Milton W. Talbot, Jr.
Department of Pediatrics, Malone and Hogan Clinic-Hospital Foundation, Big Spring, Tex.

Introduction

The problem of the irritable, hypertonic, and unhappy infant, with its accompanying problem of distraught and unhappy parents, is one which accosts the pediatrician all too frequently. It appears in any practice devoted in whole or in part to children, without apparent regard for social status or racial background, and presents one of the more difficult circumstances in the day-to-day management of children. Although a large proportion of unhappy babies may be relieved through the determination of the related problems of nutrition, general health, or cerebral injury, there remain a large number who defy explanation or management. It was toward the assistance of these children, who present the syndrome of irritability without apparent cause, that the tranquilizing effects of reserpine were applied.

The syndrome of irritability and hypertonicity, if such a term may be applied to the rather varied symptomatology involved, defies precise and accurate definition. Throughout the literature, it is usually described rather than defined. It may be said that these children usually present a combination of marked unhappiness; frequent, insoluble, and unexplained periods of crying and fretting; some degree of muscle hypertonicity and irritability; disturbance of the normal patterns of sleeping and eating; lower-than-normal weight gain; and no sense of humor. They are usually between the ages of birth and 18 months—or, at least, they are encountered more frequently within those ages.

The causes of such behavior have been sought almost since the birth of the specialty of pediatrics, and, in general, four concepts have emerged. Wessel, Cobb, *et al.*,[1] in a recent review of the literature of colic and paroxysmal fussing in infants, catalogues these four principal theories of their origin: (1) allergy; (2) congenital hypertonicity; (3) physiological immaturity of the intestinal tract; and (4) transfer of tension from the parent to the infant.

Source and Classification of Material

It being the object of this paper to analyze the results of the use of a drug in a syndrome of such varied conceivable origins, an earnest attempt was made in the selection of its materials to create as homogeneous a group as possible.

It was decided to eliminate all infants below the age of six weeks, because of the incidence of paroxysmal fussing and colic at this age which remits spontaneously. Further, the markedly variable response of the fussy newborn to formula changes, atropinization, sedation, and other maneuvers make the introduction of a new agent difficult to evaluate. It is also after this age that the more troublesome and persistent aspects of this syndrome begin to emerge.

For further reasons of homogeneity and to exclude their more varied psychological backgrounds, infants beyond the age of 12 months were not included.

All infants presenting the problem of irritability and hypertonicity in the combined office practice of two pediatricians were subjected to a routine devised to eliminate all apparent causes of the condition. Thorough physical and laboratory examinations excluded physical illness or defect. The feeding techniques employed, the formulary and dietary regimens were examined, corrected if faulty, and any nutritional deficiencies repaired. If the complaint survived these measures, the child was empirically placed on a soybean formula and an elimination diet. Skin testing was carried out by the group allergist where indicated. Those infants remaining were then considered candidates for the study, provided they had no history of convulsions (febrile or otherwise), or severe neonatal anoxia, and presented no physical evidences of cerebral damage, either traumatic or congenital.

These cases were further tabulated under the following headings:

(1) *Age.* The ages varied from 7 weeks to 11½ months, the largest group (46 per cent) from the ages from 4 through 6 months (FIGURE 1).

(2) *Duration of symptoms.* All 32 cases were described or observed to have been excessively irritable since birth. All were colicky, fussy babies in the first six weeks and, in general, the symptoms had persisted or seemed to increase.

(3) *Birth order.* Twenty-four cases (75 per cent) were first-born children as compared with the percentage of only 37 per cent in the normal run of practice in the concerned age groups (FIGURE 2).

(4) *Family history of irritability.* Of the eight cases who had siblings, four reported similar behavior in one or more at the same age. No attempt was made to determine the existence of such behavior in either parent through the

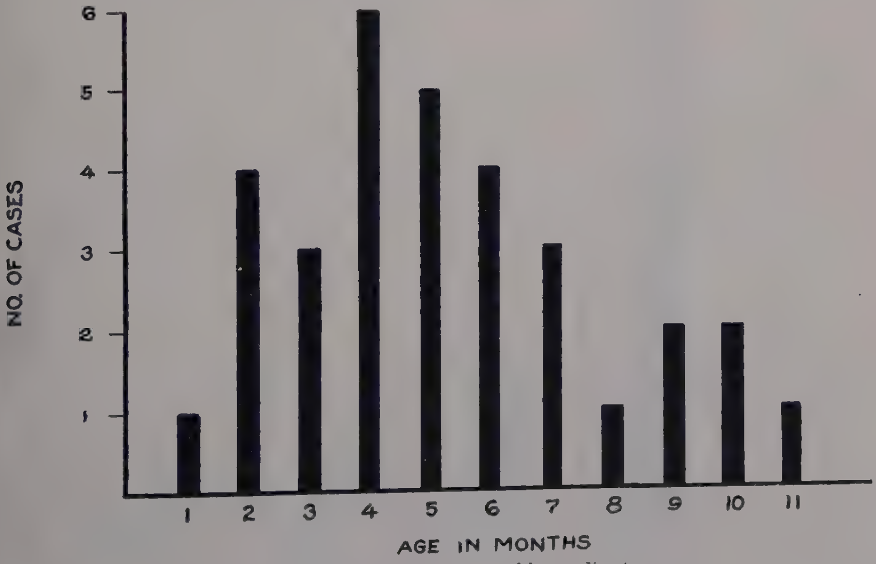

FIGURE 1. Distribution of case material according to age.

considered unreliability of the data. None of the parents involved was an epileptic.

(5) *Emotional stability of the mother.* A purely subjective rating of the apparent maternal emotional stability resulted in our classifying three of them as highly unstable and immature, the remainder being of average stability.

The 32 cases considered eligible for the study were further examined and evaluated in terms of their major symptomatology:

(1) *Irritability.* The designation of an infant as irritable was based upon impressions gained by the examiner and the parent, and by evaluating the infant's general behavior. The mother was asked to record, for one week prior to the onset of treatment, the number and duration of the periods of crying, the cause of the crying, and what measures were required for relief. On the basis of these data, 4 children were considered to be mildly irritable, 18 moderately so, and 10 markedly irritable.

(2) *Hypertonicity.* The evaluation of hypertonicity was performed by the author subjectively on the basis of general muscle tone, persistence of startle

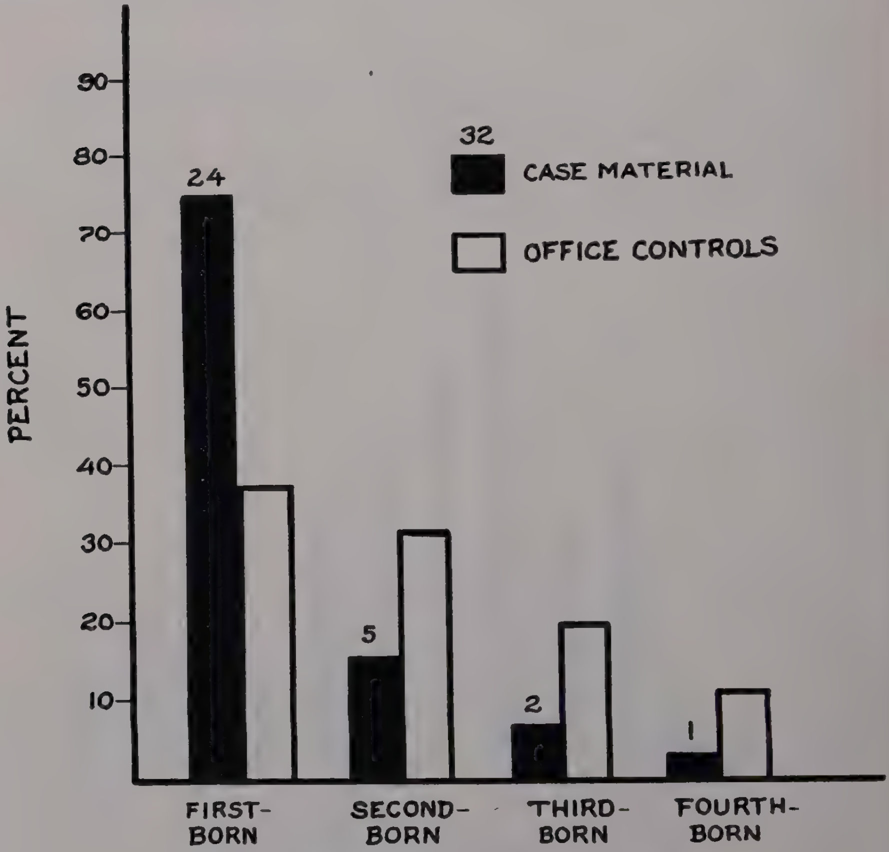

FIGURE 2. Distribution of case material according to birth order.

pattern, general activity during examination, activity of the peripheral reflexes, and motor response to the stimuli of noise and motion. Of the infants studied, 19 were considered to present little or no hypertonicity, 11 moderate, and 2 were severely hypertonic.

(3) *Sleeping patterns.* Twenty-one cases displayed patterns of sleeping which could be considered abnormal. Nine had erratic and variable periods of sleep. Twelve slept less than 10 hours daily, 4 less than 7 hours. Thirteen demonstrated extreme restlessness during sleep and, in all 21, nocturnal sleep was punctuated by periods of crying which varied from 4 to 8 times per night.

(4) *Eating patterns.* Twenty-two mothers reported deviations of eating habits from normal, eight of which were considered to be severe. Five of the children had no routine of feeding time even though four months or more of age. Twelve stated that feeding was time-consuming and created considerable tension. Eight children consumed what was considered to be a calorically below-average diet, but could not be induced to eat more. Four children ate more food than the caloric average for the age and demanded frequent feedings, although the weight was not excessive.

(5) *Weight and rate of gain.* The weights of all children for their age ranged from the 3rd to the 60th percentile, with the mean at the 38th and the median at the 40th. There was a weight-length disparity in all cases, with the mean 12 percentiles below the mean for length.

Methods

Each of the 32 children, after preliminary evaluation, was placed on reserpine in the form of an elixir (Serpasil Elixir, Ciba) containing 0.2 mgm. per fluid dram. Initial dosage of 0.1 mgm. three times daily regardless of age or weight was begun and revised upon the appearance of intolerance or unwanted side effect at the time encountered.

Each case was re-evaluated at the end of the first, the third, and the sixth week. The dosage was increased or decreased each time until effective control without side effect was obtained.

At the end of six weeks of therapy, the administration of reserpine was discontinued, and the child was re-evaluated in one to two weeks.

Ten normal children representing the age range of the study were selected from the same practice and placed on the same routine of therapy for a period of two weeks. These children served as controls.

Results

Of the 32 infants treated with reserpine, 29 were considered benefited by the drug. One patient was not helped and, in two, the drug was discontinued because of the side effects.

Dosage. With only two exceptions, the initial dosage of 0.1 mgm. three times daily was reduced by half at the end of the first week. This was reduced further to 0.1 mgm. nightly in 10 cases, while 7 cases were controlled on 0.05 mgm. twice daily. The remaining 10 required an increase in dose to 0.05 mgm. three times daily. Two children required higher dosages than that originally given, one receiving .2 mgm. twice daily, and the other 0.2 mgm. three times per day. In no case was higher dosage found to be necessary for adequate control. These doses ranged from 0.005 mgm. per kilogram per day to 0.12 mgm. per kilogram per day (FIGURE 3).

The dosage employed was not intended to indicate a minimum effective dose, but rather the amount of reserpine effective for the children concerned at which no observable side effects were encountered.

The birth order of the child had no effect upon dosage nor upon effects of the drug, nor did the degree of maternal stability.

Adverse reactions to the drug. Two children, age three and one-half and four months, were withdrawn from the study after manifesting severe abdominal cramping after every dose of the medication until the dosage was reduced to .025 mgm. in three divided doses daily. At this point, no tranquilizing effects were noted after one week.

Six children in the group were considered benefited, and three of the control infants required reduction in the initial dosage because of abdominal cramping. All were successfully maintained on the lesser dosages.

Three children developed nasal stuffiness during the first week which was controlled by a lower dosage, with successful control of the irritability being maintained.

In no case, including two on doses of 0.6 mgm. and 0.4 mgm. daily. was excessive somnolence noted, and this result was never a cause for adjustment of dosage or discontinuance in either case or control.

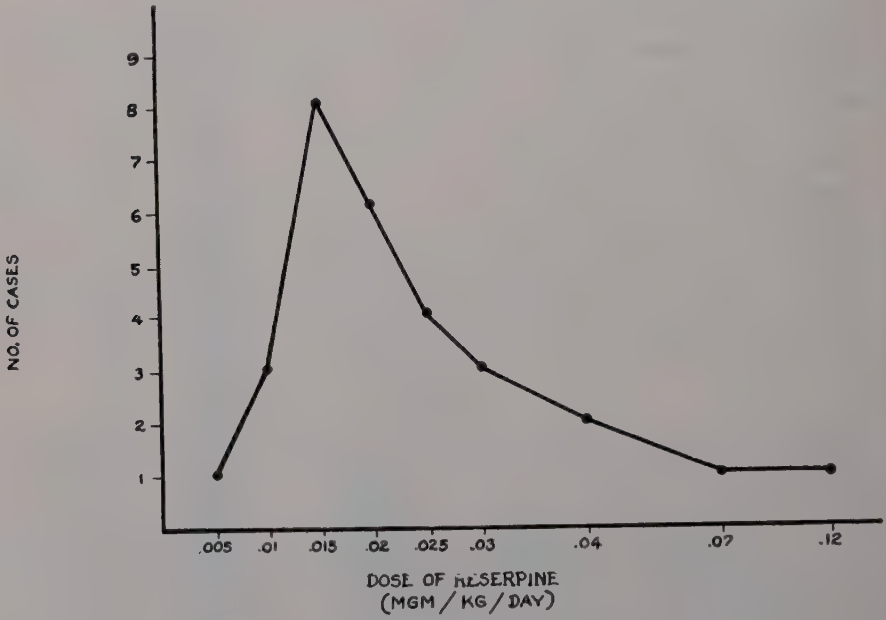

FIGURE 3. Dosage of reserpine employed in relation to weight.

In only one case, the failure, was diarrhea noted. This symptom appeared at grossly excessive dosage.

Failure. The one child who was not benefited by the drug was unchanged in behavior on dosage of reserpine up to 0.9 mgm. daily. At this level, abdominal cramping, diarrhea, and nasal stuffiness appeared. The dose was maintained at this level for four days before discontinuance. The child, six months of age, was the second child of an emotionally stable mother. His symptoms consisted of severe irritability and hypertonicity, moderately altered sleep patterns, and poor feeding habits. No effect on any aspect of the case was observed, except an increase in the total hours of sleep.

Successful control. Of the 29 infants who completed the study with successful results, 19 were considered to be returned to normal behavior, 7 were markedly improved, and 3 moderately so. These 29 cases presented an inconsistent combination of symptomatology, the varying degrees of which, in each case, makes positive evaluation of reserpine on the syndrome as a whole difficult. The response must thus be considered in the light of the effect of the drug upon the principal components of the syndrome.

(1) *Effect of reserpine upon sleep patterns.* The 21 infants with sleep disturbance were sleeping normally by the first visit after reserpine was started. This effect on the sleep behavior was perhaps one of the most emphatic and uniform results of the drug. It was one of the first noted and was one of the easiest maintained. It is to be emphasized that these children were not somnolent. They maintained a regular predictable pattern of sleep and, in all cases where simple hunger or wetting was not the obvious cause, the nocturnal awakening and crying disappeared. During their waking intervals and periods of play, the children gave no suggestion of being sedated, and the time awake was comparable to the normal controls of the same ages.

(2) *Effects of reserpine upon irritability.* The second most obvious effect was the remission of irritability. Two of those infants considered moderately irritable were withdrawn from the study because of intolerance. The one failure was considered to be extremely irritable at the outset. In all other cases, the degree of irritability was markedly ameliorated. Only three cases retained any degree of irritability after full dosage was established, and this manifestation consisted of easy and frequent crying, and failure to play spontaneously when left alone. Even in these cases, however, the effect of the drug was pronounced.

(3) *Effects of reserpine upon hypertonicity.* The effect of reserpine upon hypertonic motor activity was quite variable. In general, there was a lessening of tense behavior and a return of hyperreflexia toward normal. However, those infants demonstrating the most marked degree of increased muscle tone were the least benefited. Those children that showed a high degree of irritability, as well as of hypertonicity, were helped principally in the reduction of irritability and return to normal sleep.

(4) *Effect of reserpine upon eating patterns.* In general, these children became easier to feed. The time involved and the tension engendered at feeding became less. Those whose diets were considered calorically inadequate re-

turned to normal consumption. The five who conformed to no routine became more predictable in meal time. The eight initially presenting serious feeding problems were considered to be behaving normally at the completion of the study. The four children who ate excessively at the onset continued to do so at its completion.

(5) *Effects of reserpine on weight and rate of gain.* At the end of six weeks, the weights, in comparison to age, showed a mean increase from the 38th to the 48th percentile. In all cases, the weight-height disparity decreased (FIGURE 4).

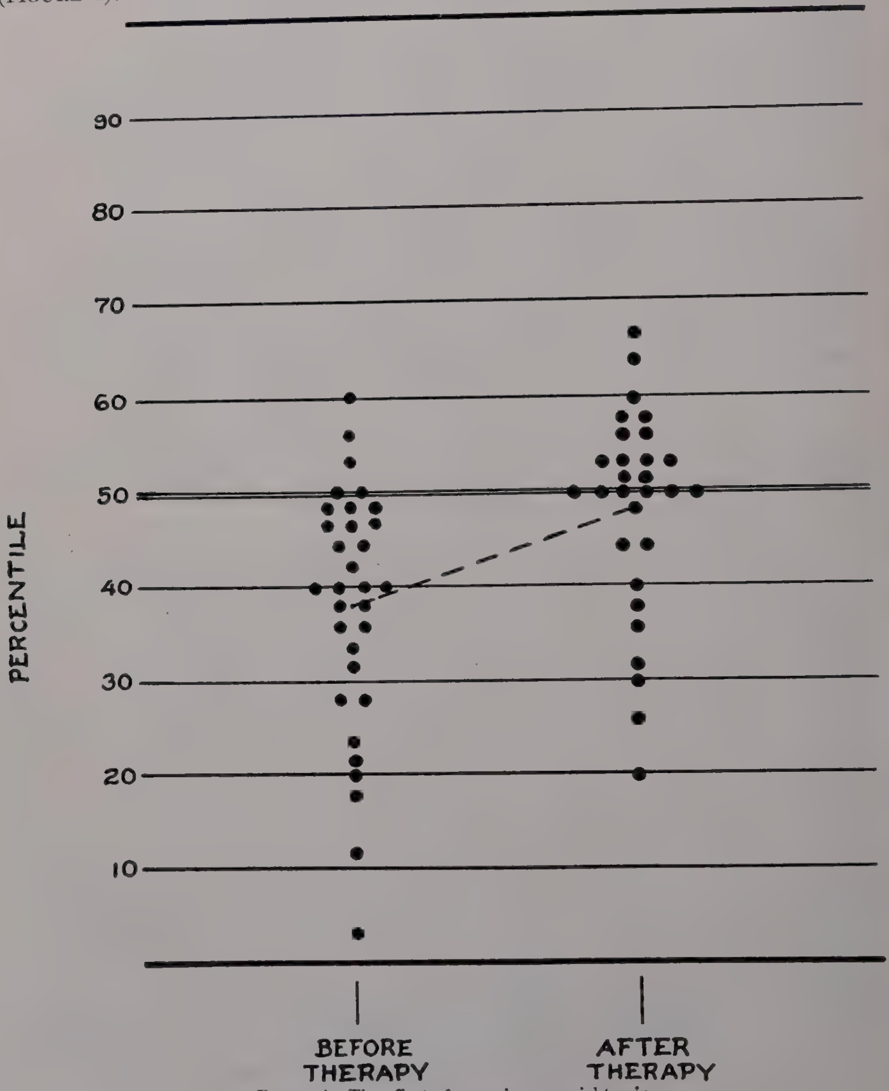

FIGURE 4. The effect of reserpine on weight gain.

(6) *Effects of reserpine upon family tension.* Although not specifically an effect upon the patient, the administration of reserpine to these irritable and unhappy children resulted in a definite and sometimes dramatic change in family tension. Both the parent-child relationship and the interparent relationship showed some degree of improvement in all cases. There was definitely observed an improvement in the sense of adequacy of all mothers in caring for their children. The parents, through more sleep and more time to perform other household activities and avocations, became better adjusted to their child and to each other. There were in this study several instances in which the mother voluntarily stated that she wished that the child had not been born. In all four cases where this rejection was observed, whether in cause or effect of the syndrome, we felt that the happier, quieter, and less demanding infant was loved and accepted to a markedly greater degree.

The effects of withdrawal and substitution. At the end of six weeks on effective doses of reserpine, the children were withdrawn from the drug. Of the 29 infants, 19 returned to the identical behavior patterns present prior to therapy. This release effect was apparent in 4 cases in 36 hours, and in all 19 in 5 days. Of the remaining 10 cases, 5 became more irritable and slept less, but not to the degree noted at the beginning of the study. The remaining 5 retained their treatment behavior, even after two weeks.

The 19 infants who reverted to pretreatment behavior were given a placebo liquid identical in appearance to the reserpine without change in their behavior after one week. All were then returned to their effective reserpine dosage, the initial results being observed once more.

The controls. The 10 children presenting no evidence of hypertonicity or irritability who were used as controls demonstrated only an increase in the total hours of sleep. No effect was noted on the weight gain in the two-week period, no effect was apparent on the activity of the child during waking hours, and none on eating habits. The control children essentially did not respond to the drug except in greater sleep.

Discussion

The effects of reserpine are difficult to evaluate in a situation in which so much depends upon subjective impressions. It is apparent that the drug is effective in eliminating the symptoms to varying degrees and, in many instances, all manifestations of the syndrome. It is also apparent that the remission of some characteristics is dependent, in large part, upon the control or attenuation of others. Thus, the observed effects bear consideration with regard toward their source.

Previous reports, for example, of the use of reserpine in adults have shown no change in their weight.[2] The weight gain noted in these infants is easily attributed to the restitution of normal patterns of sleep and to an improvement in the regularity and pacificity of feeding. It is also evident that some reduction in the observed irritability of the child is a consequence, in turn, of better nutrition and adequate sleep; and, likewise, that improved sleep results from lessened irritability. Thus there is a large degree of interaction of the effect of one symptom upon another that confuses the results of reserpine upon the whole problem.

When one considers the eight irritable children who presented no disturbances of sleep, however, it is seen that the reduction of their irritability was equally as marked as in those in whom sleep was disturbed. This was also true in those in whom the dietary complaints were minimal, and in the several irritable children who presented neither sleep nor feeding problems. It may be assumed that reserpine has a specific action in these children in reducing irritability per se.

The appearance of increased sleep span in the controls and the change from abnormal to normal sleep patterns in all infants—regardless of their symptomatology—suggests a similar conclusion in the problem of disturbed sleep.

The same conclusion is again apparent in the action of reserpine upon hypertonicity. Although it was perhaps the least affected aspect, the diminution of muscle tone observed in the hypertonic children was independent in some degree of the accompanying manifestation of irritability.

The conclusion is thus suggested that the effects of reserpine upon the irritability, sleeplessness, and hypertonicity apparent in the syndrome can be attributed to its action upon a common origin. In considering the causative circumstances in 48 newborns with colic and paroxysmal fussing—situations strictly analogous to the syndrome of irritability in this older age group—Wessel[1] considered family tension largely responsible in 46 per cent, allergy in 12.4 per cent, allergy and family tension in 18.6 per cent, and unknown circumstances in 23 per cent. The attempt was made—successfully, it is felt—to exclude the problem of allergy in this study. The prominence of family upheaval and anxiety in all cases in this series points strongly toward the thesis that the origin of the syndrome of irritability, in all its manifestations, is in the transfer of these tensions to the child. This thesis is qualified, however, by the observation of the marked decrease in these parental anxieties and tensions after reserpine had markedly ameliorated the behavior of the child. This creates the impression that, in most cases, the family tensions were largely the result, rather than the cause of the problem. This inference is also supported by the observation that all except 10 children returned to their pretreatment behavior once reserpine was withdrawn. They did so in the time interval usually seen for the subsidence of reserpine effect and were not helped by placebo therapy. It is beyond contention that parental anxiety and tension contributed to the severity of all cases, and may have been wholly responsible in the five who did not revert after reserpine withdrawal. It is also asserted that the period of reserpine tranquility accomplished much in the reduction of these tensions and established a period in which better parent-child relationships were established.

The remaining facts point, however, toward a more organic origin of the syndrome. The conceptions of a congenitally hypertonic trait of personality and of a physiologic immaturity of certain portions of the infant anatomy seem more adequate explanations in these cases. The actions of reserpine upon the syndrome of irritability may be tentatively attributed to a sedative effect upon a congenitally acquired defect or a physiologic immaturity of the centers of autonomic control or of their function. To distinguish between the two concepts, prolonged follow-up of these and similar cases must be accomplished, and the continuing, constant effects of a trait or defect observed against the probable subsidence of the picture with maturation.

It was the conclusion of Wessel[1] that, of the irritable infants in the neonatal period, most of them were responding to environmental stress in an intensity determined by constitutional factors. The corollary seems valid here: that the majority of these cases depend upon a constitutional inadequacy, the intensity of reaction being dependent upon environmental stress.

Regardless of the degree to which the origin was constitutional or environmental, reserpine provided dramatic relief in remitting the syndrome of irritability in the 29 of the 32 cases studied here. Its effects were prompt and almost universally apparent in controlling the major symptoms presented. It was safe, and its side effects were minimal. Reserpine may thus provide the physician with a tool with which to correct one of the more vexing problems of his practice and to offer distraught and anxious parents a new happiness with their children.

Acknowledgment

The author gratefully acknowledges the cooperation and assistance of Doctor J. M. Woodall in providing cases for inclusion in this study and in the preservation of data on them.

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THE USE OF RESERPINE IN OFFICE PSYCHIATRY: PRELIMINARY REPORT

By Frank R. Drake and Franklin G. Ebaugh
Denver, Colo.

Extracts of the roots of *Rauwolfia serpentina*, a shrub growing wild in India and in other tropical and subtropical regions, have been used in India for centuries as a "cure" for manic types of psychoses, as a sedative, as a fever-reducing medication, as a remedy for snakebite, as a "cure" for dysentery, and as a drug for promoting uterine contractions. In 1952, a Ciba research team[7] first identified a new crystalline alkaloid which was given the generic name of reserpine. Its Ciba brand name is Serpasil. Pharmacologic and clinical studies have shown that reserpine is the chief active principle of *Rauwolfia*. Recent reports in the literature on both laboratory animals[12] and human beings[4, 6, 11, 14, 15] have given convincing evidence that reserpine has a tranquilizing effect on patients and that it produces a mild sustained lowering of the blood pressure and a slowing of the pulse rate.

As a result of these researches and of other studies[5, 7] and of the Ciba announcement that reserpine has been found effective in a wide variety of neuropsychiatric conditions, it was considered important, if not urgent, to investigate the value of this new alkaloid in office psychiatry. A total of 40 private psychiatric office patients were treated with oral reserpine for periods varying from one week to six months. Prior to the administration of the drug, each patient was informed that reserpine has been found to be effective in many different psychiatric conditions and that it might very well prove to be of benefit to him. He was given a short description of the possible side effects of the drug and advised to get in touch with us if he developed any of them. All of the patients were initially administered 0.25 mg. of reserpine after each meal, and were asked to report their progress to us in person, by letter, or by telephone at weekly or bi-weekly intervals, until the proper dosages were stabilized. We used reserpine to augment the conventional psychiatric therapies, especially psychotherapy.

The psychiatric conditions and situations in which reserpine was used were as follows:

(1) *Character neuroses.* There were three cases in this group. An emotionally unstable farm boy said, "The pills keep me calmed down and keep my temper down. If I don't take them I feel like telling someone off. I sleep better when I take them. In the daytime, I can't sit down and relax without them." The second case was a 48-year-old housewife who has suffered from a severe lifelong paranoid personality. When she became suspicious of her husband's fidelity, she developed tension headaches, tremors of the hands, and insomnia. There was no associated depression. She has been taking 0.75 mg. of reserpine daily for the past five months, and reports that the drug makes her more relaxed and allows her to sleep better. The third case was that of a 35-year-old janitor who has always had trouble accepting advice and guidance from authorities because his father had been cruel, alcoholic, and, apparently, had

had no love or affection for him. He lost his job about once every year following a fist fight with his boss. He requested help because of increasing tension with marked tremors of his hands. His dosage of reserpine was reduced from 0.75 mg. to 0.25 mg. of reserpine daily over a one-month period. He has taken 0.25 mg. daily for the past five months. He said, "The tablet I take after breakfast seems to help me take things better without getting so mad."

(2) *Anxiety states with minimal or no depressive features.* There were nine patients in this group. Eight of them showed moderate to marked improvement on dosages varying from 0.25 mg. to 2.5 mg. of reserpine daily. In describing how reserpine seemed to affect them, they used such expressions as, "The tablets keep my stomach from tying in knots"; "While I am on Serpasil my thoughts and fears don't bother me. I feel good in spite of them"; "They seem to relax me when I am nervous or jittery"; "Whenever I run out of Serpasil my tension headaches come back"; and "Since taking the drug I feel better and don't have those goofy spells (anxiety attacks)." The only patient in this group who did not seem to benefit from reserpine was a 27-year-old married female who was partially incapacitated by a chronic anxiety state with hysterical conversion features referable to the genitourinary system. Over a period of two months, she was tried on dosages of reserpine varying from 0.75 mg. to 2 mg. daily. She showed no improvement and, in addition, developed a mild diarrhea. Hence, reserpine was discontinued.

(3) *Anxiety states with depressive features.* None of the six patients in this group showed any apparent diminution in their depressive reactions in spite of the use of 0.125 mg. to 0.75 mg. of reserpine daily for periods of time varying between three weeks and two months. In addition, three of these six patients complained of a feeling of sleepiness with the stated doses of reserpine. One patient not only complained of feeling "slowed down and sleepy" with reserpine but also stated that the drug had no effect on the intensity or frequency of his obsessive thoughts.

(4) *Schizo-affective (depressive) disorders.* Only two of the seven patients in this group seemed to demonstrate any improvement in the depressive component of their illness. Typical remarks of these patients were: "Even when I take only 0.125 mg. of reserpine daily I become so sleepy that I can't function effectively"; "I can't notice any difference whatsoever"; "When I am taking reserpine I feel much less irritable and easier to get along with, but feel just as depressed"; and "I'm just as down in the dumps and have the same unreal feelings whether I take the drug or not." One patient who responded to reserpine fairly well said, "As long as I take four of the tablets (1 mg.) every day, I feel less depressed and more able to cope with my problems and don't give up quite so easily." The following two cases of this group are of particular interest:

The first case is a 38-year-old single woman who has been chronically and seriously depressed for over three years. She has refused electroconvulsive therapy as well as hospitalization of any type. During a six-week period, while she was taking 0.5 mg. to 1.5 mg. of reserpine daily, she experienced no relief from her depression. She said, "The only difference which I notice while I am taking Serpasil is that I can sit in a chair and jitter and think of suicide rather than walking back and forth thinking about it." One evening she took 35 Serpasil tablets (3.5 mg. of reserpine) in a suicidal attempt. The only apparent result was that she slept soundly for 12 hours without awakening and felt lethargic for about three days. There was no change from the normal in her blood pressure or pulse rate.

The second patient, who is equally interesting, is a single 31-year-old schizophrenic male who has been seen in psychotherapeutic interviews one to four times weekly for the past nine months because of severe anxiety and depression. His parents will not allow hospitalization or any of the somatic therapies, in spite of the fact that he has suffered from several panic states with associated suicidal ideation. For the past six months, he has regularly taken 0.25 to 0.75 mg. of reserpine daily, with satisfactory control of mild to moderate symptoms of anxiety. However, on three occasions during this period he developed symptoms of panic. The panics have been controlled by increasing the frequency of psychotherapeutic interviews as well as by immediately increasing the dosage of oral reserpine to 0.75 mg. four times daily. Within about 48 hours after the increase in dosage to 3.0 mg. daily, he develops what might be called the "reserpine state," which is characterized as follows: (1) generalized slight slowing of all voluntary bodily movements, with no apparent decrease in muscle coordination;[10] (2) continued presence of the usual emotional conflicts and fears, without the usually associated physiological and motor responses; (3) an appearance of being relaxed and sleepy; (4) drooping of both upper eye lids;[15] (5) miosis;[15] and (6) shallow respirations.

Each panic lasted about one week. There was no evidence that the daily 3.0 mg. dosage of reserpine reduced the duration of panic. It merely seemed to place the patient in a drug-induced "deep freeze" as far as reacting to his acute fears and conflicts was concerned, and made him more amenable to psychotherapy.

(5) *Tension states following somatic therapies.* Eight of the nine patients of this group derived moderate to excellent improvement in their tension states while on reserpine for one to three months. The following two cases of this group deserve particular attention:

The first is a 63-year-old housewife who was given 10 electroconvulsive treatments as therapy for a paranoid schizophrenic reaction. Her blood pressure initially was 195/100. She has taken 1 mg. of reserpine daily for five months, which includes two months of hospitalization. Her blood pressure at present is 150/85. Although she still has the same delusional system as on original admission to the hospital, she has been so thoroughly "reserpinized" that she no longer develops incapacitating anxiety and can live comfortably at home.

The second patient is a 73-year-old widowed arteriosclerotic female who received eight electroconvulsive treatments for a severe depressive reaction a few months ago. She was known to be intolerant even to very small doses of the commonly used sedatives. For the first month after her discharge from the hospital (during which time she could not participate in psychotherapeutic interviews because her home was in another state), she reported no amelioration of her residual anxiety and mild depression from the ingestion of 0.5 mg. of reserpine daily. Hence, the drug was discontinued.

(6) *Hypomanic reactions.* There were only two patients in this group.

One is a 43-year-old rancher suffering from a prolonged mild hypomanic reaction. He has taken 0.75 mg. of reserpine daily for five months. His wife states that it would be intolerable for her to live with him if he did not take the drug, "which makes him calm and easier to get along with." The other patient is a 47-year-old single female who has suffered from manic-depressive reaction of alternating type for many years. Recently, she was treated successfully with 1 mg. to 3 mg. of reserpine daily over a four-month period of mild hypomania, and was able to continue her job as a journalist. Then the characteristic depressive phase of her illness appeared, and 3.0 mg. of reserpine daily were completely ineffective in controlling it.

(7) *Reactive depression.* The only patient in this category is a 47-year-old married male who was operated on for a glioblastoma multiforme of the left temporal pole several months ago. Two months ago, he suddenly became overwhelmed with the hopelessness of his prognosis and became agitated and suicidally depressed. Hospitalization was not considered indicated, as his previous history showed a strong tendency toward chronic invalidism whenever he was placed in such a dependent situation. His dosage of reserpine, which had been 1 mg. daily for the previous month, was immediately increased to 0.75 mg. after each meal and at bed time; *i.e.*, to 3.0 mg. daily. He remained at home with his wife constantly at his side for the next 48 hours. By that time, he was relaxed and in what we call the "reserpine state," as previously described. For the next two weeks, he was brought to the office for psychotherapeutic interviews on six occasions. Since he seemed to improve over the following 10 days, his reserpine dosage was reduced 0.25 mg. daily until he was once again on the 1 mg. regime. Blood pressure and pulse remained the same throughout the episode.

(8) *Agitated depression.* The only patient in this classification is a 69-year-old obsessive housewife, who received an inadequate number of electroconvulsive treatments for an agitated depression in another state in June 1954, as she became fearful of the whole procedure. Two months ago, the severe agitation and depression reoccurred. She refused hospitalization and appropriate treatment. She was placed on 4.0 mg. of reserpine daily and kept on this dosage for one month. Not the slightest improvement in her clinical condition resulted. Blood pressure remained at 160/90 and no change in pulse rate was observed. The "reserpine state" did not develop in this patient.

(9) *Stammering.* The only patient in this category is a 22-year-old single male with a lifelong history of severe stammering, based on unconscious fear of expressing hostility. For the past two months, he has taken 0.5 mg. of reserpine daily, with considerable obvious improvement in his speech. He looks and feels more relaxed than ever before.

(10) *Hysterical aphonia.* The only patient in this category is a 44-year-old married male who has not been able to speak above a whisper for 20 years. He has been examined in many of the best clinics in this country and no organic cause for his affliction has ever been discovered. Historical evidence, as well as psychological tests, point to an unconscious fear of expressing hostility as the source of his speech difficulty. He has taken 0.5 mg. of reserpine daily, 0.25 mg. after breakfast and 0.25 mg. at bedtime for the past three months,

with marked improvement in the intensity and clarity of his speech. He stated that he cannot take over 0.5 mg. daily because of resulting drowsiness.

Comments and General Discussion

When using oral reserpine on private psychiatric office patients, it is well to keep in frequent contact with them by telephone, if possible, to be sure that side effects of the drug do not cause them to stop taking the drug altogether, and also to insure that a sufficiently high dosage is being administered to give them maximum therapeutic results. The judicious raising or lowering of the dosage at the proper times during the first two or three weeks of treatment will greatly benefit the patient. Parenteral reserpine is probably rarely indicated in office psychiatry, because of the reported rapid drop in blood pressure, the increased incidence of side effects, and the danger of precipitating a psychotic reaction.[6] We used oral reserpine entirely.

Oral reserpine was very effective in the eight anxiety states which were characterized mainly by the presence of "free floating" anxiety symptoms. This fact has been reported previously by others.[1, 3, 5, 15] One patient whose chronic anxiety was largely somatized to the genitourinary system was not benefited by reserpine. Oral reserpine was comparatively ineffective in all six neurotic anxiety states with prominent depressive features. The more such anxiety states were complicated by depressive features the less likely was reserpine to be effective in alleviating the symptomatology. We were not able to verify the finding of Noce, Williams, and Rappaport[8] that "depressed patients become alert and sociable" on reserpine. All three cases of character neurosis derived considerable benefit from reserpine, presumably because their anxiety reactions were mainly based on a fairly "pure culture" of repressed hostility and resentment, without the associated guilt, self-condemnation, and depression which are so common in the "pure" affective disorders. There was no evidence, however, to indicate that reserpine reduces the tendency of these "psychopathic personalities" to "act out" their emotional conflicts. The drug merely reduced the physiological symptoms of anxiety.

Only two of our seven patients with a schizo-affective disorder showed a diminution of depression while on reserpine. One patient with recurrent suicidal panics was successfully reduced to the "reserpine state" three times, as an emergency measure to decrease the possibility of suicide. The other five patients were not improved by oral reserpine. [Note: The authors propose the term "reserpine state" for that condition of oversedation with the drug which might conceivably be expected to diminish the likelihood of the crystallization of suicidal thoughts into actual suicide. Although we utilized this technique with oral reserpine alone, it would probably be preferable to initiate it with parenteral reserpine in order to expedite the onset of the "reserpine state." The main indication for this type of oversedation in office psychiatry should be those rare but frustrating occasions when a severely depressed patient (or his closest relative) refuses to accept hospitalization or outpatient electroshock therapy. Unless such noncooperation is temporary, however, the psychiatrist has the right to withdraw from the case.]

The six cases of schizo-affective disorder whose depressions were treated successfully by electroconvulsive therapy derived great benefit from the anxiety-reducing property of reserpine in the immediate posthospitalization period. The same good result was obtained after electroconvulsive therapy of a case of severe reactive depression in a patient with a cyclothymic personality. Similar benefit occurred with the use of reserpine in the postelectroconvulsive period of a successfully treated case of agitated depression in a senile patient. The only formerly depressed patient whose postelectroconvulsive anxiety symptoms could not be satisfactorily controlled by reserpine was a 73-year-old patient whose original condition was an agitated depression, at least partly of organic origin. One 69-year-old female patient with an agitated depression was treated with 4.0 mg. of oral reserpine daily for one month and showed no improvement. The "reserpine state" could not be attained, at least on the dosage used. One 47-year-old patient with a severe reactive depression which began several months after an operation for glioblastoma multiforme of the left temporal pole was successfully reduced to the "reserpine state" by increasing his daily reserpine dosage to 3.0 mg. He remained on this dosage until psychotherapeutic efforts seemed to decrease the danger of suicide.

One mildly depressed and ambulatory schizophrenic patient with compulsive hand-washing about 30 times daily reported that reserpine reduced the intensity of the recurring impulse to such a degree that it was no longer a problem to her. Reserpine, however, had no beneficial effect on her depression. One patient who suffered from a neurotic depression, as well as from obsessive thoughts of a disagreeable nature, originally reported a decrease in the amount of emotional disturbance which he experienced from the thoughts. After a few more weeks on 0.75 mg. of reserpine daily, however, he stated that the drug had no effect on the frequency or the emotional disturbance caused by the obsessive thoughts.

Two mildly hypomanic patients were successfully treated with oral reserpine. This result is in line with the findings of other studies.[2, 8, 14] The patients were sufficiently controlled to allow them to continue with their regular occupations. One of them was well controlled on 1 mg. to 3 mg. of reserpine daily for 4 months. Then, with the onset of a characteristic depressed phase, reserpine was completely ineffective. We did not feel that the reserpine caused the depressed phase, as she had had such phases before, following hypomanic phases. On the other hand, we believe that reserpine caused mere symptomatic improvement of hypomania rather than a real alteration of the disease itself. In addition, we found no evidence to indicate that reserpine shortens a hypomanic phase. One patient afflicted with severe lifelong stammering displayed considerable obvious improvement in his speech after taking 0.5 mg. of reserpine daily for one month. One patient with hysterical aphonia showed a similar improvement with the same dosage. It seems probable that the favorable effects in both of these cases were simply due to the well-known tranquilizing and sedative effects of reserpine.

Side Effects

As was expected,[5, 9, 13, 15] no serious side effects from the use of reserpine occurred in our series of patients. Sleepiness, the commonest complaint, occurred in six patients. Five of these patients had similar complaints after the dosage had been reduced to 0.125 mg. of reserpine daily for a period of time varying from two to four weeks, and asked if they might stop taking reserpine. All five of this group of patients were suffering from mild to moderate depressions, three in association with neuroses, and two with schizophrenia. The sixth patient, who complained of sleepiness, was a male patient with hysterical aphonia of many years' duration. Since the intensity and clarity of his speech improved considerably while on 0.5 mg. of reserpine daily, he was quite willing to accept the nonincapacitating sleepiness and continued on the medication.

Nasal congestion was a complaint of two patients with neurotic depressions who had been taking 0.75 mg. of reserpine daily for four weeks. Since neither of these patients seemed to be deriving any benefit from reserpine, they requested that it be discontinued. Only one patient developed a mild diarrhea, which seemed to be due to reserpine. She was a young housewife whose chronic anxiety had become somatized primarily to the genitourinary system. After two months on 0.75 mg. to 2 mg. of reserpine daily, no improvement in her clinical condition occurred and the medicine was discontinued.

Thus, it is apparent that the patients who admitted or complained of side effects of reserpine were almost entirely among the group who derived no benefit from the drug in the first place.

Conclusions

Forty private psychiatric office patients were treated with oral reserpine for periods of time varying from one week to six months. Each patient had a preliminary thorough history, physical examination, and appropriate psychological tests. No sweeping conclusions may be drawn from this preliminary study because of the small number of patients involved and the short period of therapy with reserpine. Certain trends were noted and discussed, however, which will require more research and time before final clarification and firm criteria can be established. In the future, it is anticipated that satisfactory control studies will be established. The only control data we can offer at the present time are the result of previous and concomitant experience with similar clinical disorders.

Even at this time, one can say that reserpine seems to be a valuable adjunct to psychotherapy and to the other conventional psychiatric therapies, in certain psychiatric illnesses. One should not discount, however, the suggestibility and the subjective factors in the use of any new drug. It is also no easy matter to determine how much improvement is due to psychotherapy alone and how much to reserpine. At least, the "reserpine state" appears to be a definite response entirely due to the drug. Serious untoward reactions to the small doses of oral reserpine such as we used will probably never occur and need not be feared. The unusual type of sedative effect which reserpine causes should be a source of inspiration for further research by all branches and fields of medicine and the medical sciences.

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THE USE OF RESERPINE IN PRIVATE PSYCHIATRIC PRACTICE

By Sydney Kinnear Smith
University of California, Berkeley, Calif.

In 1665, Nathan Hodges, Fellow of the Royal College of Physicians, published his conclusions on therapeutic measures employed to combat the plague that had recently ravished London.[1] He considered Snake Root as the most effective drug so employed, stating that it is "deservedly accounted most efficacious." Amazingly similar to research findings of the last few years is his statement that "it is agreed by all that the more subtle particles collected together and diversed of the grosser and unprofitable parts became more efficacious in medical cases." John Quincy,[2] who wrote the preface to Hodges' book, published an *English Dispensatory* in which he listed Serpentar (Snake Root), saying that its "warmth occasions it to be useful in *nervous disorders*." Whether Hodges may be considered the first physician in private practice to publish the results of Serpentar therapy in nervous cases is open to question. The first English dictionary[3] published in this country (1788) lists Serpentar as a "medical root." This suggests that it may well have had its place in our armamentarium in the Colonial period.

In the relatively brief span of its more recent use, particularly in its psychiatric implication, a considerable literature has appeared relative to reserpine. Reports have been based upon studies of *institutionalized* groups at a *psychotic* level. There appears to be a need for recorded experience of its use in *private practice* with *nonpsychotic* patients. The present paper is concerned with 50 cases encountered in private psychiatric practice currently receiving reserpine (TABLES 1 and 2).

The plethora of articles in popular magazines and in newspapers has given the impression that reserpine is a "cure" for insanity. No such claim has been made by medical investigators nor by the organization that made it available. As a result of this early and overenthusiastic publicity, it is not unusual for patients to be startled when its use is suggested by the psychiatrist in private practice. The fear of insanity that so often takes them to the psychiatrist has been augmented by their reading. Illustrations that appeared in widely read publications suggested a close parallel to Bedlam, of Shakespeare's day.

The cases here reported have contributed to the formulation of conclusions on the nature and action of reserpine (Serpasil). They are based upon detailed material that is here summarized in the interest of brevity.

Therapy, begun in May 1954 and continued to the present time, was planned for a group of the *anxiety states*. To these were added several of the compulsive-obsessive neuroses, together with a few borderline cases. Among these were three paranoid states and three manic-depressive psychoses that necessitated private hospitalization. Physical examination, associated with laboratory studies, including electrocardiograms, preceded the onset of medication. Psychiatric observation and blood pressure reading have been recorded weekly, together with the comments of the patients and, frequently, of their relatives.

The majority of the 50 patients, 23 male and 27 female, were between 25 and 35 years of age, with extremes of 19 and 79 years.

Reserpine has been used orally in most cases. Parenteral medication was employed in cases of an acute nature. Dosage has been one to three milligrams daily. Six persons received electroshock therapy preceding, or concurrently with, reserpine.

The action of reserpine is basically the same in treatment of psychotic and nonpsychotic individuals. The underlying psychopathology, differing as it does, necessitated modification in dosage and in the technique of administration. The statistical summary indicates *differences of response* in the several *diagnostic groupings*. In the *anxiety states*, improvement appeared in from two to eight days. "Side effects," a matter of concern in the anxiety states, did not appear, or were unnoticed in the compulsive group. The paranoid states showed little interest in "side effects." In the latter groups, concern over transient physical discomfort was overshadowed by the greater interest in their obsessive or persecutory formulations.

TABLE 1

STATISTICAL SUMMARY OF 50 CASES RECEIVING RESERPINE*

Diagnosis	Anxiety states	Compulsive	Paranoid personalities	Manic depressive	Post partum pt.	Miscellaneous	Remarks
Number of cases	35	4	3	3	1	4	
Sex							
Male	18	3	3	2		3	
Female	17					1	
Age (aver.)	31	28	44	51	22	49	Limits 19–79
Blood press. (aver.)	128/70	123/75	138/74	149/84	118/65	136/70	3 hypertensives included
Dose	1–3 mil.	1 mil.	1 mil.	2 mil.	4 mil.	4–6 mil.	
Side effects	29			2		2	
Onset	2–12 d			15–18 d	2 d		
Duration	7–24 d			5–36 d			
Results							
Improved	28	3	2	2	1	3	
Minimum change	7	1	1	1		1	

* Serpasil (Ciba).

TABLE 2

REASONS FOR MINIMUM IMPROVEMENT IN 11 CASES

Anxiety states	7: Exacerbations of depressive trend, 4; reduction of dosage by patient, 1; apparent drug, idiosyncrasy 1; gradual increased blood pressure in hypertensive, 1
Compulsive neuroses	1: Nature of compulsion interfered with repetition of medication
Paranoid personality	1: Persecutory formulation involved medication
Manic-depressive psychoses	1: Reserpine discontinued due to increased depression
Miscellaneous	1: Lack of cooperation, although hypertension was reduced after first 2 weeks of therapy (alcoholic)

In a study of this nature, *differences* should be stressed as *supplementing* the conclusions of previous investigators, *rather than repeating* them. It is with this attitude that the following observations are made:

(1) Reserpine has a beneficial effect in the treatment of nonpsychotic and prepsychotic cases in the private practice of psychiatry.

(2) Improvement is slower than has heretofore been reported in the treatment of psychotic cases. The onset of lessened tension, decreased anxiety, and the appearance of a more benign attitude, varies. Even a small change *may* not be apparent until several weeks after the start of treatment in cases of this type. Optimum benefits may not be reached before two or three months. The "slow" nature of the drug was stressed by Wilkins[4] in 1952 and had been recognized in prior Indian reports.[5] Wilkins suggested that this slowness might be one of its most characteristic features. Immediate beneficial changes cannot be anticipated in the treatment of nonpsychotic cases, although a few exceptions were encountered. Whether such exceptions were the result of the drug or of the power of suggestion is open to question. *Final* judgment as to its effectiveness should not be passed under three months. The immediate and often spectacular changes are more characteristic in the treatment of acute psychoses than in the psychoneuroses, particularly of the anxiety type. The tendency to initiate treatment with a larger dosage in the psychoses may partially account for this quicker effect.

(3) Side effects play a more important part in the treatment of *psychoneurotics* than they do in *psychotics*. While they are easily controlled by dosage regulation, their appearance and brief duration is a matter of greater concern to the psychoneurotic. Occurence rate is higher in individuals too alert to physical symptoms and prone to misinterpretation. Time consumed in allaying their fear is considerable, but certainly essential in private practice. This concern is capable of changing the patient's attitude towards the therapeutic agent—a change that may be of importance.

(4) *Indoctrination* of prospective patients, a routine in all cases where feasible, has been a valuable part of the treatment regime. The patients were told in simple terms, aided by charts, about the nature of the drug, about anticipated results, and about the transient aspect of possible side effects. An interest in treatment was the usual response. The *real* sedative action of reserpine was contrasted with the immediate and temporary action of the barbituates. *Knowledge* supplanted *fear* if side effects appeared, a point of much greater importance in the psychoneurotic than in the psychotic. Discouragement was reduced if the beneficial results were not immediately forthcoming. Indoctrination made the patient a *co-observer* with the doctor and paid dividends in cooperation. Some most enlightening observations resulted from this practice. Indoctrination, especially valuable in the private practice of psychiatry, merits a much wider use in the field of medicine. A patient who understands the nature of his treatment is a better therapeutic risk than one that takes a pill "because the doctor says so." The comment of one patient that she was having "Salvador Dali" dreams expressed more graphically the nature of reserpine dreams than any that has yet appeared in the literature.

(5) Electroshock therapy gave an improved response when combined with

reserpine in the few instances that it was used. Lessened resistance to treatment is a contribution of the drug to private practice. The patient's attitude may change the entire treatment, or may result in its discontinuance. Complete absence of postconvulsive excitement was striking, and may have significance in private practice. It has been this factor that has made electroshock therapy (E.S.T.) impractical for office use. Few offices are equipped to cope with it. Ambulatory patients have been treated on outpatient status in private hospitals. From their point of view, the familiar, noninstitutional aspect of the office would have made treatment less of an ordeal. Seven E.S.T. cases (not included in the current study) were given reserpine for one to two weeks before E.S.T. There was no fear of the treatment, no postconvulsive excitement, and no traumatic complications. These cases could have been treated in any office. Reserpine is a real adjunct to E.S.T. Its ability to *replace* electroshock is open to question. Conclusions in this connection are premature, and are not warranted until sufficient time has elapsed in which to evaluate comparative results.

(6) Patients with anxiety states, particularly those with a minimum of depression, have shown a weight increase. Lessened tension, with improved digestion, makes this understandable. Decreasing insomnia is another indication of diminished tension. In private practice, where family attitude may be essential to successful treatment, the weight and sleep factors are important. Family-patient confidence both in treatment and in the physician may hinge on these more obvious signs of improvement.

(7) Administration of reserpine, both parenteral and oral, resulted in immediate improvement in one acute manic psychosis. Electroshock had produced no result, although this patient has responded to it during two previous manic episodes. The former recovery rate had been slow, and there was no reason to anticipate the almost total recovery in three days.

(8) Two depressive psychoses, together with many anxiety states having depressive components, responded to reserpine with a prompt increase in depression. One of the psychotic depressions was continued on treatment despite the intensified depression. In four weeks, the added load had lifted, and the depressive syndrome cleared more quickly than could have been anticipated. As the patient later said, "it was worth it to get well so soon." The same pattern has been followed in the anxiety states, associated with depression. These findings would seem to indicate that, if reserpine is continued, the depressive exacerbations are temporary. The implication of this finding, if substantiated by continued studies, may add materially to our understanding and use of the drug in the depressive states. Therapeutic fortitude may supplant the current attitude that reserpine has little value in depressions, if not contraindicated.

(9) Intensity of the recurrent compulsion, characteristic of the obsessive-compulsive state, has been diminished after the onset of medication. In turn, accessibility has given the opportunity of carrying out a more satisfactory therapy. It would be difficult to express in medical terminology the nature of the sequence more tersely than did one patient, recently a State Department member. In reference to the change in compulsive intensity, he remarked

"Co-existence is possible now." He was beginning to appreciate the value of tranquility, insight, and accessibility personally, if not internationally.

(10) A comparable response has been observed in several prepsychotic individuals with paranoid trends. Their formulations became progressively less fixed, and they were more receptive to an objective interpretation.

Summary

The results of diminished tension and anxiety, associated with an improved accessibility to psychotherapy, is of particular significance in private practice. In its final evaluation, this may be the dominant contribution of reserpine to psychiatry. We may be entering a New Era because of a better integration between the several schools that constitute our specialty. The Couch may yet be moved from the Ivory Tower to the Temple of Aesculapius.

Acknowledgments

Appreciation is expressed to Doctor Richard H. Roberts, of the Research Department, Ciba Pharmaceutical Products, Inc., San Francisco, Calif., for technical assistance and for specimens of *Rauwolfia* roots, and to Payne Thebaut, long-time member of the Walt Disney staff, for aiding greatly with his cartoon, used in the Indoctrination plan for patients.

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THE USE OF RESERPINE IN CERTAIN NEUROLOGICAL DISORDERS: ORGANIC CONVULSIVE STATES, ENURESIS, AND HEAD INJURIES*

By Vasilios S. Lambros
Arlington Hospital, Arlington County, Va.

(1) *Organic Convulsions*

In the field of neurology, a real satisfaction is obtained when a convulsive is completely controlled. Many times, however, this victory is an empty one, as a certain amount of irritability, moodiness, or personality changes continue unaided by the treatment. The families return to the neurologist to assist them in overcoming what has now become their major problem. The neurologist's only recourse, up to the present, has been to increase the amount of anticonvulsant medication. This treatment leads to more of the same irritability or moodiness and to an increase in the unpredictability of the patient's personality and of his reaction to his environment.

The known effects of the *Rauwolfia* preparations on personality, mood, and irritability prompted a clinical trial in different convulsive disorders.

From a group of about 700 convulsives with whom we had been working at the time, we were able to obtain a total of 220 cases that were good examples of the irritability, moodiness, and personality variables which we have just described. It must be emphasized that these were private cases. Accordingly, the cooperation was excellent.

The majority were of the major convulsive type. The remainder were psychomotor, *petit mal*, and variants of minor seizures. One hundred and four were adults and 116 were below the age of 14.

In the normotensive adult group, no alteration of blood pressure was noted at any time. In the associated hypertensive, the blood pressure was reduced to a satisfactory level. The children did not show any material changes in blood pressure. Blood-pressure readings were registered in the sitting position.

Significant bradycardia and miosis were not observed in any of the patients.

Serial electroencephalographs, totaling 397, failed to reveal any significant specific pattern which could be ascribed to reserpine. The inference is drawn that reserpine has no effect on the human electroencephalogram.

There was no apparent synergistic effect of hypnosis or sedation with any of the anticonvulsants. The whole root preparation was used prior to the appearance of reserpine. In the early cases, the average dosage varied from 150 to 400 mgm. The dosage of reserpine varied from 0.25 to 1.50 per day. It was found that many of the side effects could be obviated by giving the greatest portion of the dosage at night. Medication has been continuous for at least 3 months and up to 14 months. Placebos were interchanged and maintained for four weeks without the knowledge of the patient or family. The regression was quickly apparent. Recovery was usually delayed about one week.

Relatively few side effects were noted. These cases included one of nausea accompanied by diarrhea. Reserpine had to be discontinued. This effect would be repeated whenever the patient was placed on reserpine. One patient developed a looseness of the bowels. She eventually had to discontinue the reserpine, although she had materially benefited by its use. Eleven patients had a hypnotic or sedative effect which was controlled readily by a reduction in the amount, or rearrangement in time, of the reserpine given.

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* The reserpine (Serpasil) used in these experiments was supplied by Ciba Pharmaceutical Products, Inc., Summit, N.J.

In 67 cases, we were able to reduce the amount of anticonvulsant medication without any recurrence of convulsions or alterations in the electroencephalographs. It is our belief that these patients were overmedicated.

Thus, out of 220 cases, 218 were improved by the use of reserpine. The immediate and lasting effects of reserpine were a constant and predictable personality. The tranquility was noticeable and corroborated by the families, friends, and co-workers.

(2) *Head Injuries*

In head injuries, the hyperirritability and restlessness that ensues is extremely difficult to control. The predominating causes of these irritative phenomena are as follows: (1) the irritation of the cortex and the meninges by free blood; (2) the actual injury to the brain substance, gray or white, either by edema with its anoxia and reduced efficiency, or by hemorrhage, with its attendant destructive effect, or by impairment of the blood supply by laceration or thrombosis of the affected blood vessel; (3) the sudden release of lower centers with their subsequent mismanagement of the vital chemical-physical and mechanical functions of the body; and (4) the variable interruption of hormonal secretion as manifested by injuries to the master gland, the pituitary.

With the use of the usual medicaments to allay such irritative phenomena, there are varying degrees of associated changes in the neurological signs and symptoms and, in the normal dynamic physiological factors such as state of consciousness, pulse, and respiration. These changes may or may not be misleading to the trained observer. They do impose an additional burden, however. The quest for a medication which would not depress bodily functions nor produce neurological changes through its effect seems to be fulfilled to an extent by reserpine.

A total of 19 cases forms the basis of this preliminary study, 14 of which are head injuries. Nine of these cases were below the age of 14. Associated with the head injury, there were 5 cases which had linear fractures. Two had compound depressed fractures. There were 5 cases of postcraniotomy.

Cases with the diagnosis of cerebral concussion, which by definition is a momentary physiological interruption of the cerebral processes without any histological changes or clinical signs, and in which recovery is rapid and complete, were excluded.

For clarification, the group of cerebral contusion and/or laceration which were treated is defined. Cerebral contusion and/or laceration is an organic interruption of the cerebral processes, as manifested by petechial to gross hemorrhages, localized or generalized edema, and microscopic or macroscopic tears of the brain substance. The extent of abnormal neurological signs or symptoms is dependent on the area or areas involved. Recovery is retarded and dependent wholly on the scope of the damage.

Reserpine was initially given intramuscularly in all cases. As soon as nausea and vomiting were controlled, or consciousness regained, the oral route was used. Amounts varied from 20 mgm. to 1 mgm. per 24 hours. Medication was given for 3 to 5 days. All blood pressures were recorded at 45 degrees. Following the immediate period of shock, the blood pressure was stabilized around 90 to 110 and showed relatively little fluctuation in 12 cases. There were two which showed a variable response. In one, the blood pressure, in spite of the reserpine, was so fluctuant it was quite disconcerting. The pressure would range from 180/130 to 50/30. The other case was immediately stabilized, but gradually dropped to 80/40 by the third day. Complicating this case, however, was an aspiration bronchopneumonia and azotemia with gradual renal failure. It is our belief that the complicating factors were liable here instead of the reserpine.

Pulse and temperature, in all cases, stabilized and returned to within normal limits in a much shorter period of time than in a comparable group which was treated with the usual array of sedatives. Temperature, in 13 cases, returned to normal by the third day. The exception was the case with the azotemia and bronchopneumonia, which showed a secondary rise on the third day.

The restlessness and hyperirritability in all cases subsided more rapidly than in the comparable group which did not receive reserpine. No masking or additive neurological signs or symptoms were observed. Urinary incontinence seemed to be decreased. Consciousness was regained relatively early. Mental alertness was surprisingly good. One had the over-all impression that the abnormal neurological signs and symptoms regressed much more quickly. Miosis was not observed in any of the 14 cases. Happily, the complaint of headache was negligible. All patients were discharged without headache. In their subsequent office visits, no patient voluntarily offered the complaint of headache. On questioning, the patients stated they had some mild headaches but none of any severity. The average hospital stay was nine days.

Five cases of postcraniotomy received reserpine routinely for three days. As with the head injuries described above, the blood pressure, pulse, respiration, and temperature stabilized rapidly. Hyperirritability and restlessness were much allayed. Surprisingly, these patients complained relatively little of headache and required very little specific medication. The dosage varied from one to five mgm. Sedation was not required. The response at times was dramatic and, on the whole, very gratifying.

On the basis of the above cases, it is our feeling that reserpine will, indeed, be a useful adjunct in the treatment of head injuries and postcraniotomies.

(3) *Enuresis**

Enuresis has been a problem from the ancient days. As all will agree, the relief sought is simple. Yet there are many modes of treatment, and all are ineffective. As reserpine has been shown to have a definite effect on the afferent stimuli to the hypothalamus, the highest center of the autonomic nervous system, it was felt that reserpine could possibly exert a braking effect on the bladder, thereby preventing the involuntary emptying of the bladder during sleep.

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* With the collaboration of Doctor Fernando R. Leyva.

This paper is a preliminary report of 17 consecutive cases of chronic enuresis which were treated with reserpine. Nine of these had an associated hyperkineticism. Nine electroencephalograms were taken. Three of these were normal, and six showed nonspecific diffuse abnormalities.

Surprisingly, 16 cases stopped wetting the bed within three nights. The one failure was X rayed. A reduplication of one ureter was found. This control continued for at least 3 months, one being controlled for 10 months. To our dismay, however, with the onset of the Christmas holidays, 10 of the 16 cases did not maintain their medication. Enuresis recurred in these cases. The six who maintained their medication continued under complete control. The dosage for this group averaged 1.50 mgm. In the 10 cases in which enuresis recurred, placebos were used for three weeks without any noticeable improvement. Following this treatment, the patients were placed on their previous dose of reserpine. To date and on this basis, we have had complete failure in six, partial control in three, and in only one has complete control been regained. The reasons for such a high percentage of failures cannot be accounted for. The average dose for this group was 0.75 mgm. Why this dosage was adequate in the beginning and inadequate the second time bears further investigation. We shall try these cases on a higher dosage and shall report further.

It is interesting to note that many authors reporting on large series of institutional cases, although no specific facts were correlated to incontinence, had the definite feeling that, as a whole, incontinence was reduced markedly. A similar correlation was made by us in our small series of head injuries.

PRELIMINARY REPORT UPON THE EFFECT OF RESERPINE ON EPILEPSY AND BEHAVIOR PROBLEMS IN CHILDREN

By Frederic T. Zimmerman and Bessie B. Burgemeister

College of Physicians and Surgeons, Columbia University; and the Division of Child Neurology, the Neurological Institute, New York, N. Y.

Introduction

This paper is a preliminary report of our findings to date on the effect of reserpine* in a group of children and adolescents with severe behavior disorders, many of whom suffer from convulsive seizures or are mentally retarded.

On the basis of preliminary clinical observations, it appeared that results might be highly individualized. Intensive study of these cases seemed desirable, using a variety of approaches, and we have attempted to integrate data from various aspects of the problem so as to estimate the action of the drug in producing physiological and psychological changes in behavior and the mechanisms underlying these overt manifestations of change.

Materials and Methods

Selection of cases. Eighty-seven children and adolescents familiar to us for a period of years were selected for study and have been followed in the present study for an interval of almost one year. All of these patients fall within the age range of from 3 to 16 years.

Seventy-two of the patients suffer from epileptic attacks of the *petit mal*, *grand mal*, or psychomotor types, while 15 are mentally retarded. Of the 15 mentally retarded children, 3 also have *petit mal* or *grand mal* attacks. These were divided into *Group I*, 72 patients having convulsive seizures without mental retardation; and *Group II*, 15 mentally retarded patients.

Methods. Group I: Within our group of epileptic patients, results were evaluated in the following terms: (1) the anticonvulsant action of reserpine in reducing or controlling seizures; (2) the action of reserpine in alleviating trigger mechanisms which precipitate convulsive seizures; and (3) the effect of reserpine on behavior.

Group II: In our group of children and adolescents who are mentally retarded, we were interested not only in the effects of reserpine on behavior, but in trying to determine mechanisms underlying this behavior, so as to discover personality traits and patterns most responsive to treatment with the drug. It seemed to us that such an investigation, concerned with individual differences in intellectual and emotional makeup, was one requiring intensive and individual depth study, rather than one involving a broader survey of group behavior on a more superficial level.

In dealing with a drug such as reserpine, which has a multiplicity of reported effects, we felt that only by concentrated study on a small series of cases thoroughly known to us over a period of years could drug effect be distinguished from individual variability of response. Our unique and wide experience with intellectually and emotionally retarded children made such a concentrated preliminary study in depth possible.

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* Reserpine (Serpasil) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

The children selected for our preliminary study with reserpine were pupils in a good private boarding school (The Algonquin School, Saranac Lake, N. Y.). In this way, the environment was not only held constant, but more favorable conditions were obtained by removing emotional entanglements often found when these children live at home with parents. Quantitative evidence on the effect of the drug was evaluated in terms of improvement in verbal intelligence, performance tests scores, Rorschach patterns, speed and accuracy of reaction, new learning resulting from reduction of emotional interference, *etc.* Qualitative evidence of behavior change was obtained by clinical observations, ratings of teachers, and anecdotal material. Two types of controls were also used in this experiment: (1) the testing psychologist and teachers were uninformed as to whether a placebo or reserpine was given (actually all cases received reserpine); (2) a comparison of previous scores on the same individual cases over several years of testing was made to see if a particular subject rated within, below, or above his usual test, retest variability range.

Dosage. Group I: All patients with convulsive seizures received medication ranging from 0.25 mg. to 3.0 mg. of reserpine daily (1 to 12 tablets), depending upon the individual case. Small initial doses were given, and the drug was gradually increased up to the point of individually optimal dosage. The average daily dose was 1.25 mg.

Group II: In our group of mentally-retarded children, we decided to use an arbitrary intial dose of reserpine of 0.5 mg. daily for all patients. Eight of the 15 children remained on this dose for six months. However, since preliminary observations of behavior indicated that one month was sufficient to note clinical changes, we increased the daily dosage by 0.5 mg. a month for each of three consecutive months. Following a standard dosage of 0.5 mg. for the six months' period, therefore, these eight patients received 1.0 mg. daily during the seventh month of treatment, 1.5 mg. daily during the eight month, and 2.0 mg. daily during the ninth month. In the remaining seven cases, a daily dose of 0.5 mg. was given for the first month, 1.0 mg. daily for the second month, and 1.5 mg. daily during the third month and thereafter.

Psychological testing was done before each dosage increase, with retesting at the end of each step before the dosage was again increased by the next 0.5 mg. increment. In this way, we were able to determine more readily the optimal dosage needed to produce psychological change and, at the same time, to observe the effects of too low or too high a dosage in individual cases.

Manometric recordings were taken at intervals of one month. These recordings fell within the range of normal variability, no significant alteration in blood pressure being noted for any case in our series.

Recording of Convulsive Attacks (Group I)

The number of convulsive attacks was recorded daily on a calendar chart by the parents and data were transcribed to a duplicate sheet for recording and analysis each time the patient returned for a visit.

Results as to seizure control.

Diagnostic Classification	Number
Petit mal only	11
Petit mal and *grand mal*	41
Grand mal only	16
Psychomotor	4
Total	72

From TABLE 1 it will be seen that, while there was no improvement in weekly incidence of attacks for the group as a whole, detailed analysis of individual responses shows that the combination of reserpine with previous medication has some therapeutic effect (5 to 99 per cent reduction of attack frequency) for 31 per cent of the total of 44 cases. Thirty per cent were unimproved and 39 per cent were worse during combination therapy.

TABLE 2 shows actual worsening for the group as a whole, but 12.5 per cent of the eight patients showed some therapeutic response (5 to 79 per cent reduction of attack frequency). Twenty-two and one half per cent of the group showed no response, and 65 per cent showed increased frequency of attacks during reserpine therapy alone.

TABLE 3 shows that again there was no improvement for the group as a whole, while 13 per cent of individual cases showed partial control, 54 per cent were practically unchanged and 33 per cent showed increased seizure frequency upon combination therapy.

Combined treatment in four cases of *psychomotor epilepsy* produced no improvement in any instance.

Results as to alleviation of trigger mechanisms precipitating convulsive attacks. In some of our patients, there were detected trigger mechanisms which seem to

TABLE 1

COMBINED TREATMENT, RESERPINE AND OTHER DRUGS, IN 44 CASES OF PETIT MAL SEIZURES

Group results	
Average weekly attacks on previous medication	114
Average weekly attacks on previous medication and reserpine	116

(Reserpine average daily dose 1.25 mg. for average duration of 13 weeks)

Individual results	%
Complete control of attacks	0
Practical control (80–99% reduction in attacks)	4
Partial control (35–79% reduction)	27
(5–34% reduction)	0
No significant change (0–4% reduction)	30
Increased frequency of attacks	39
Toxic side effects	17

(Reserpine average daily dose 1.25 mg. for average of 13 weeks)

TABLE 2

TREATMENT WITH RESERPINE ALONE IN EIGHT CASES OF PETIT MAL SEIZURES

Group results	
Average weekly attacks on previous medication	15
Average weekly attacks on reserpine medication alone	32

(Reserpine average daily dose 1.25 mg. for average duration of 10 weeks)

Individual results	
	%
Complete control of attacks	0
Practical control (80–99%)	0
Partial control (5–79% reduction)	12.5
No significant change (0–4% reduction)	22.5
Increased frequency of attacks	65
Toxic side effects	12.5

(Reserpine average daily dosage 1.25 mg. for average duration of 10 weeks)

TABLE 3

COMBINED TREATMENT IN 57 CASES OF GRAND MAL SEIZURES

Group results	
Average weekly attacks on previous medication	5
Average weekly attacks on previous medication and reserpine	7

(Reserpine average daily dosage 1.25 mg. for average duration of 9 weeks)

Individual results	
	%
Complete control of attacks	0
Practical control (80–99% reduction)	0
Partial control (5–79% reduction)	13
No significant change (0–4% reduction)	54
Increased frequency of attacks	33
Toxic side effects	20

(Reserpine average daily dosage 1.25 mg. for average of 9 weeks)

precipitate attacks under special conditions. These factors (anxiety, rage, *etc.*) seem to set off attacks—especially in *petit mal* cases—when otherwise the patient is fairly well under therapeutic control. It is a common experience to have parents report a series of attacks in the previously well-controlled youngster around Christmas time, at a birthday party, or under similar conditions of stress. Having in mind the "calming" effect of reserpine, we tested its activity in children whose attacks already had been reduced maximally by standard medication.

TABLE 4 shows that, of nine cases of *petit mal*, four were better, four showed no effect, and one was worse with addition of reserpine to the regime. Of the *grand mal* cases, one was improved, four were unchanged, and two became worse. One patient having unclassified attacks was practically controlled with combined therapy.

Among the total of six cases showing reduction in attack frequency on combined treatment, no single trigger mechanism predominates, and it is suggested that the action of reserpine in alleviating triggered responses may be broad in scope and its individual effect determined by the characteristics of a given case.

Effect of reserpine on behavior of epileptic children. In this aspect of our study we were interested in reported qualitative changes in behavior after the administration of reserpine to patients with convulsive disorders.

Six of the 10 cases (TABLE 5) so studied showed behavior improvement with reserpine therapy and, in 3 cases, this was concurrent with reduction in attack frequency.

In four cases, behavior was less satisfactory than before reserpine administration and, in four of the cases showing increased seizures, less satisfactory behavior was observed. This last we believe to be a result of toxic side effects of reserpine. It is a common finding that toxicity of anticonvulsant drugs and increase of seizure rate are positively correlated.

Toxic signs noted in Group I.

	Number of cases
Depression and irritability	2
Lips blistered or swollen	2
Headache	2
Gastric distress	1
Ataxia	1
Silly laughter	1
Diarrhea	1
Hyperkinetic activity	1

When toxic signs appeared, medication was either reduced or discontinued entirely. Sometimes it was possible to resume very small doses of reserpine and work up to an optimal dose without the appearance of toxic side reactions after it had been reduced or discontinued initially.

Mentally Retarded Patients (Group II)

In addition to observations of behavior and ratings by teachers and staff members, verbal and performance scales were included in our battery of tests because they offer a means of measuring changes in underlying mechanisms of behavior expressed overtly as speed of reaction, accuracy, memory, form perception, abstract thought, new learning resulting from a reduction in emotional interference, *etc.* These included Merrill-Palmer, Pintner-Paterson, Wallin A Peg Board, Wallin B Peg Board, Seguin Formboard, and picture-puzzle tests.

We also gave our mentally retarded children some projective techniques, including the Rorschach inkblot test, in order to study underlying motivations, techniques for handling anxiety, adaptiveness, general adjustment, *etc.*

TABLE 4

EFFECT OF RESERPINE IN ALLEVIATING TRIGGER MECHANISMS WHICH PRECIPITATE CONVULSIVE ATTACKS

Case no.	Type of attacks	Average weekly attacks		Category of results	Reserpine	
		Premedication alone	Reserpine added		Duration of treatment	Average daily dose
1	PM	88	31	Partial control	9	0.75
2	PM &	57	45	Partial control	8	1.5
	GM	1	32	Worse		
3	PM &	6	3	Partial control	4	0.5
	Jacksonian	4	4	No effect		
4	Unclassified	154	27	Practical control	10	1.25
5	PM	62	60	No effect	11	1.0
6	PM &	45	46	No effect	9	1.25
	GM	1	1	No effect		
7	PM &	7	10	Worse	9	0.75
	GM	9	8	No effect		
8	PM	122	115	No effect	11	1.0
9	GM	4	11	Worse	12	1.25
10	PM &	11	7	Partial control	8	0.75
	GM	2	2	No effect		
11	PM &	62	67	Worse	11	1.5
	GM	5	2	Partial control		

TABLE 5

Case No.	Effect on rate of attacks	Av. daily dose (mg.)	Behavior changes reported while on reserpine
1	Worse	0.25	Very hyperkinetic
2	Worse	1.5	Very restless
3	No effect	0.75	Calmer—angry less often
4	Partial control (72%)	0.75	More relaxed—less tense—does not get excited so easily—doing well in school
5	Worse	0.75	Laughing excessively
6	No effect	0.75	More reasonable—concentration better—follows instructions better in school
7	No effect	0.25	Remarkable change—quiet—tractable—civilized—"Fury of his activity is gone"—change apparent in two days—nursery school startled by sudden change in behavior—appetite much better—sleeps better
		0.5	Hyperactive—speech garbled—disconnected and thick
		0.375	Too excited and will not listen at all—wild
		0.25	Behavior improved but not as good as initially
8	Worse	1.0	Very depressed—irritated—crying a lot
9	Partial control (49%)	0.75	Appetite improved—tried to feed self anything he can handle with his fingers—last time he tried to feed self three years ago—coordination better—seemed happier
10	Partial control (44%)	1.0	Appetite better—sleeps better

Seven children also were given the Stanford-Binet Test (Form L, 1937 Revision).

The reports of individual scores and of clinical observations and teachers' comments and ratings cannot be included here because of limitations of space. They will be the subject of a later publication. Furthermore, the size of the samples and the relatively brief period of investigation of such complex syndromes and functions permit us to reach only highly tentative impressions concerning possible usefulness of reserpine in mentally retarded children. These impressions are stated below.

Summary of Impressions

In our group of serious behavior problems including children and adolescents with convulsive disorders and mental retardation, we studied the effect of reserpine from a variety of approaches. Because our sample is small and the time interval relatively short, results must be interpreted with caution and inferences considered tentative.

Group I: (1) When reserpine was combined with other medication in cases having *petit mal* or *grand mal* attacks, some therapeutic effect was obtained in individual cases and seizures were reduced.

(2) In a small series of patients with psychomotor attacks no anticonvulsant effect was noted using reserpine with other drugs.

(3) Reserpine, when used as an additive after maximal reduction of attacks was first secured by standard medication, did inhibit, in some cases, those psychogenic triggering mechanisms which tend to nullify the effect of the anticonvulsant medication.

(4) In a few cases, improved behavior did follow reduction in attacks, but in the majority of cases, improvement in behavior appeared unrelated to seizure reduction.

Group II: (1) No change in verbal or performance quotients has taken place to date for our group as a whole on psychological testing, but individual cases seem to show improvement on performance tests beyond the range of test, retest variability, suggesting that faster reaction time, accuracy, and new learning may result from reduction in emotional interference.

(2) The relation between observation of improvement in behavior and improvement on psychological tests is closest and most dramatic in our sample when the subjects are out of contact and psychotic.

(3) Two cases showed less satisfactory behavior and lower psychological test scores under reserpine treatment.

(4) To date, the wide variability of responses to reserpine, aggravating the behavior problems in some children and causing improvement in others, points to a highly individualized response to the drug, which seems largely dependent upon the personality pattern of the individual case.

(5) Findings, to date, emphasize the need for further study on a larger population of children and adolescents, with special consideration of evidence from projective techniques. Psychiatric study also is indicated, and we are continuing this research along these lines.

A NEW APPROACH TO THE EMERGENCY TREATMENT OF SICKNESS CAUSED BY NARCOTIC WITHDRAWAL

By Eugene F. Carey
Department of Police, Chicago, Ill.

As a surgeon of the Chicago Police Department, I am frequently called upon to treat a sickness rare to most doctors, but common to the police, which overcomes narcotic addicts who have just been deprived of their drugs by enforcement officers.

This condition, called "narcotic withdrawal sickness," is characterized by definite signs and symptoms. Its severity depends upon the strength of the drug the addict has been using at the time withdrawal has taken place, as well as upon the location where withdrawal occurs. Apart from these causes, neither sex, race, color, nor age seems to have much or any effect. As regards strength of the drug (generally morphine or heroin), this quality will depend entirely upon the amount of, and frequency of, dilution of the "market" supply, and on the number of dope peddlers through whose hands the narcotic passes before it is purchased by the addict.

There are several ways in which withdrawal sickness may be brought on and which can govern its acuteness:

(1) *By a simple home reduction plan.* At home, surrounded by his friends or his family, the patient decides to reduce his dosage, or to go on a diet. His supply and his source of supply are good. He can govern his sickness according to his will. His mind has nothing on it but a desire to cut down his load a little. So he takes the "bite" as much as he wants.

(2) *The "market panic."* This condition follows unlooked-for pressure or a raid by enforcement officers. The source of supply is suddenly eliminated and the peddlers are jailed or scattered. Here the addict or "junkie" is faced with a great problem. Suddenly he is forced to go on "short rations." His holding supply of his drug is usually very small, and he begins to worry. Sooner or later, his worry becomes a "panic." He knows that if he runs out of the drug he cannot borrow a shot from any of his friends, even if they know it will save his life. Nor will he part with any of his own supply at any time, for he is notoriously one of the world's most miserly persons. No matter how great his supply may be, he will never part with any of it. He will invite a person to go and find himself a peddler, as he did. Hence, when an addict tells you that he got his first shot from another addict, he is lying. The truth is that he got his first shot from either a pusher or a peddler.

(3) *The cure.* Often an addict will decide to take the "cure." Usually, this act is born of his own free will, and there are two ways he can go about it. For example: either he or his family may have the means to buy his way, as a patient, into some sanitorium or, instead, he may volunteer to undertake, as a patient, some sort of governmental treatment. Wherever he lands upon the "cure route," he knows he will receive adequate care and be given either a gradual reduction treatment or else a substitute drug. In a sense, this treat-

ment amounts to a sort of vacation. Wherever he is able to go, he no longer has a care in the world. His troubles are all left on the outside. He knows he has come of his own volition, and that he may leave at his own request and convenience. It is surprising how many of these people take the "cure" because they want to hide out for some reason and, at the same time, talk about the possibilities of obtaining drugs in other towns with those who are likewise taking the "cure." Narcotic enforcement officers are prone to argue just how far away from a cure institution many of these addicts get before they again take a shot.

(4) "*Kicking the habit.*" This procedure takes place when an addict is picked up by the police and lodged in jail. He is detained in a concrete-floored, steel-barred cage or cell after he has been catalogued and screened. Then he is left to his own resources to think and to meditate. Also, there may be other addicts in the same cell with him. None knows what is next on the agenda, what is to happen to him, or where he will go. In time, the drug within each addict's system begins to wear off. One yawns; then they all yawn. Next follows lacrimation, retching, vomiting, running bowels, twitching, jerking. Their vertebral canal seems to fill with ice water, they say, and soon this chilly ache becomes an agonizing, unbearable, freezing pain, not alone in the back, but all over the body. The pain causes them to cry piteously, scream, and convulse. This condition is withdrawal sickness.

At this point, you may have begun to wonder why these narcotic word pictures should be displayed in a discussion such as this?

The reason is that I wish to illustrate the several ways in which an attack of narcotic withdrawal sickness can be brought on, and to make clear that each method, or way, can and does determine just how severe the attack will be. In each of the four ways mentioned, it is easy to see that the mental attitude of the patient plays a very important part in his sickness. Also, it gives some insight as to how the patient may feel about the onset as well as the outcome of his sickness. This attitude can and does have much to do with the whole affair. We must remember, then, that his mental attitude is of paramount importance to the addict, and that his attitude can, in fact, make or break him.

We do not pretend to know why addicts take drugs. All we have ever found out is what they tell us, namely that the taking "makes them feel normal." This phrase, of course, means that taking a drug brings about a feeling that is pleasing to the addict. It is the addict's idea of how he wants to feel. It must follow, then, that a nonaddict's feeling of normalcy would be abnormal to an addict. Hence, the addict takes his drug and, when that peculiar feeling of his norm, which only morphine or heroin or some other drug can bring about, begins to permeate his entire system, then, and only then, does he feel normal. The larger the dose, the greater becomes his feeling of normality.

You will note that we have mentioned morphine and heroin. We have done so in order to direct your attention to the fact that there are two types of addicts. Although both drugs come from the same source, each creates its own individual kind of an addict.

Morphine produces a passive type of individual, a group comprising slinking, cringing persons such as the petty thief, the shoplifter, the pickpocket, and the prostitute. When such persons steal or purloin the property of someone else, they take only enough to enable them to buy a supply of their favorite drug.

Heroin, on the other hand, develops the vicious killer who so often resorts to cruel, inhuman, lustfully barbaric sorts of crime. He may and can easily become one of the assassin type, who frequently teams up with the heavy marihuana smoker. For some unknown reason these addicts, as distinguished from morphine takers, seem to flock together. They try to look alike, as did the zoot suiters of yesterday. Today we recognize them by their tight fitting dungarees, cowboy boots, lack of hats, "D.A." haircuts and sideburns, and open zippered sport jackets.

The "ladies of the needle," too, have a peculiar quirk in their mental make-up. Perhaps their twist is not the oldest, but it certainly is one of the oddest to come down to us through the years. Long ago, the professional prostitute noted a general cessation of menses when she became an addict. This condition, she seemed to reason, would accomplish two things for her: first, it would act as a contraceptive by stopping the menstrual flow; second, it would permit a longer working month. The second idea worked out well, but the first idea did not always hold true. Consequently, many a child was born who "kicked a habit" during the first few hours of its life.

Going back for a moment, you will again note the mention of two drugs, this time heroin and marihuana. While the potentials of these drugs for activating the mental attitude are somewhat similar, their origins are far apart, as are their ways of taking hold upon a person. For example, heroin invites "addiction," as does morphine or any other of the opium series. On the other hand, marihuana invites "usage," as does cocaine. The reaction of the opium drugs, when withdrawn, invites a definite and severe withdrawal sickness whereas, in the case of cocaine and marihuana, the end results are but a transient although highly nervous condition.

An addict's definition of addiction is "It is a condition brought about by something I take that I cannot get along without, because I get deathly sick without it." Here, we see, the allusion is to a siege of sickness following withdrawal of narcotic drugs. Thus, many of us feel that the withdrawal of any thing which does not invite withdrawal sickness suggests the word "usage" rather than "addiction." It might be well to mention here that those who take cocaine or marihuana could be designated as "users," as are those who take alcohol, tobacco, coffee, *etc.*

Formerly we were able to find cocaine users more easily than we can today. Perhaps this drug has lost its popularity because marihuana is cheaper and easier to get. Cocaine may be sniffed up the nose or used hypodermically. Regardless of how it is used, whether sniffed or "main lined" directly into a vein, as heroin is taken, it is known as a pleasure "pop." The euphoria following a "pop" of cocaine is most welcome to the tired thinker, especially if he is of the type who frequently tends to sympathize with himself, as do some "big" business men, scholars, musicians, and other professional people. Sometimes the dose is taken so frequently, or is so large, that a feeling of generalized anesthesia or freezing follows. This effect invites an antidote such as morphine which, when frequently taken as an antidote, will bring about addiction.

Occasionally, we find an addict who is a "flier." The flier uses what is known as a "speed ball," which is a mixture or combination of both heroin and cocaine. He will tell you that the reason he uses such a combination is that he gets his "jolt" or effect quicker, and that it sends him "higher." This type of addict can become the most troublesome of all known drug takers, because he can, and often does, lose every vestige of sanity. As a rule, this "speed ball" is feared by nearly all who take dope, and the only reason one may possibly have for taking it is to have something to brag about when a meeting takes place with other so-called "cloud riders."

Fear is the most important concern in the life of an addict. The addict fears he may run out of the drug. He fears there may be a supply panic. He fears anything and everything that may have bearing on his drug. Will he get it? Will he not get it? Will it be too adulterated? Will it be too strong? Yes, he even fears that his drug, particularly heroin, *may* be too strong. There is a very good reason for this fear. Because of a supply panic, or anything else that may affect the market supply, the pusher or peddler begins to add more and more adulterant. As the drug becomes weaker and weaker because of this adulteration, the addict begins, unknowingly, to undergo a reduction cure. In time, accordingly, the drug he is taking *could* consist of nothing more than the adulterant, usually milk sugar. This being the case, it readily follows that if the police pick up the addict at such a time, he may have very little drug in his system, and it follows that his withdrawal sickness will be a very light attack. Hence, the interrogator's work should be lessened, and so should that of the doctor. The fear of a potential sickness, however, now overwhelms the addict and results in our having to do with an exceptionally noisy patient who is totally overcome with a self-pity and anxiety. He may now develop a needle habit and enjoy making a human pincushion of himself.

On the other hand, the fear of too strong a dose is a *real* fear, as the addict using heroin knows that too strong a dose may kill him. A strong, lethal dose of heroin is known as a "hot shot," and is usually given by the peddler to a "too-talkative-to-the-police" addict in order to silence him. "Dead men tell no tales," nor does the recipient of a "hot shot," and such a dose does not leave a clue in a body previously saturated with heroin.

All these details are known to be basic psychogenic factors which govern those who take drugs. While we have accumulated much information about those who take drugs, their habits, places of abode, where and when to find them, as well as a world of knowledge pertaining to their drugs, and so forth, nobody, not even the taker of the drug himself (be he a savant or a moron), can give you any better reason for taking drugs than that already mentioned; namely, that it makes him feel what to him is "normal."

As was said earlier, there are, in general, four causes of withdrawal sickness: voluntary reduction in the home; a market panic; reduction in a sanitorium; or reduction caused by being jailed.

We of the police department have to do only with those narcotics prisoners who receive our treatment during the few hours they are in our jail. The treatment we give is predetermined by the Federal Narcotics' Law, known as the Harrison Act. For one dollar a year, we doctors can register with the

Internal Revenue Department and, in turn, get a special tax stamp which permits us the use of opium, coca leaves, marihuana, *etc.*, in our practice of medicine, and to use them to the best of our judgment. But, says this law, in a sense,"Do not let us catch you using your judgment." This interpretation may seem amusing, but there is really nothing amusing about it. It makes one think and, when one has given it proper thought, one understands that it really means "Have nothing to do with a known addict or user of these taboo drugs anywhere at any time, unless it be in a regularly recognized institution designed and equipped to care for such patients." By following this advice a doctor will have nothing to worry about in his practice, regardless of what his specialty may be.

At our Central Police Headquarters in Chicago, we have a department set aside for narcotic offense cases. It is supervised by Lieutenant Joe Healy, who directs police narcotic activities all over the city, as well as his aides within headquarters. Two of these headquarters' aides, William Freund and Harry McMahon, are veteran narcotic police officers, and it is with these officers, who interrogate and catalogue all narcotic prisoners picked up by the police, that this author has been associated for a number of years. In their years of helping interrogate, catalogue, and detain over 30,000 narcotic offenders, both Freund and McMahon have developed very clever approaches to the several types of prisoners, and this experience, in turn, enables them better to understand and read reactions, as well as to obtain needed information.

It might be well to point out here that the law does not require that a person shall be jailed simply because he takes a drug. The real reason for his detention may be possession, peddling of drugs, robbery, or some other crime. This information comes out during interrogation and cataloguing, while the prisoner, male or female, is in detention for the few hours before being sent before the narcotics' court judge, who disposes of the case either by dismissal or by ordering a short jail term, or a long penitentiary sentence, as the case may warrant. The prisoner's detention in our police headquarters rarely exceeds 48 hours; generally, 24 hours or less.

Those of us who attend a prisoner affected by withdrawal sickness know about the Federal Act, which governs the use of drugs listed in the Act. We also know that the ideal treatment for this sickness would be a dose of the drug used by the addict. We also appreciate the fact that we are not equipped as a narcotic hospital, nor as any kind of institution or clinic intended to treat addicts. We also know that the government will not delay action long enough to permit our treating narcotic cases detained in a cell room for but a few hours, for proper treatment is a long-drawn-out program requiring recognized and adequate care. Above all, we remember that we are doctors within the police department and that we, too, are a part of the department. Even so, we must abide by the law, just as other doctors must if they wish to keep out of trouble with the government.

This being so, how, then, do we treat our narcotic addicts?

To begin with, it would be better if we were permitted to utilize any of the high-grade substitute drugs (Demerol, Dolophin, *etc.*) available today. But the sad part of this is that these drugs, which are recognized as real substitutes and are so used in proper treatment institutions, also have their usage governed by the Harrison Act. Thus they, too, are out of our reach. Nor can we send the patient to a local hospital, for no hospital will accept a narcotic case, especially one sent in under police escort.

About the most useful emergency drug applicable to our narcotic cases is a heavy dose of bromide. In order to benefit the addict, however, the dose must be very large and frequent. Here we have a drug which, because of a necessarily large dosage, will usually upset a stomach undergoing narcotic withdrawal. Then, again, we invite not only a severe bromide rash but a new habit, bromism.

Another medication used is the barbiturate. Here, too, is needed a large dosage, one that provokes a poisoning problem of its own, as well as a habit. Adding the effect of a stomach upset by either the bromide or the barbiturate to that of the withdrawal sickness does not seem to benefit the patient. The use of barbiturates, therefore, is not recommended.

A metropolitan police headquarters' lockup is not a place in which to treat a narcotic patient because there are no beds; because there is no regularly organized nursing care; because there is not time for proper treatment, the prisoner being detained for only a few hours at the most; and, finally, because there is no opportunity for the police doctors to follow up a case. Therefore, we who have to do with a passing or temporary narcotic treatment problem are ever on the lookout for, and ready to welcome, any pharmaceutical product we can lawfully use; above all, one that will cancel out the mental terrors and fears which overcome the addict when he is "freshly plucked from the tree" and brought to police headquarters, where he is faced with an attack of narcotic withdrawal sickness.

In the medical journals, some time ago, we began to find reports on *Rauwolfia serpentina* and how it was being used in hypertensive cases. After a time, we began to use *serpentina* on a few addicts who were hypertensives. Unfortunately, these prisoners had left the lockup before we got around to see them again. But, on asking another prisoner or two, as well as our interrogation men, we were told "They were all right when they left." Of course, we never fully knew from this what "all right" meant.

As time went on and the pure alkaloid reserpine was presented, we began to hear of its use in mental cases and the remarkable results obtained through its administration. This information was interesting but, somehow, we failed to compare the narcotic addict's mental problem with that of any other mental case. One day, however, we read how this new drug had calmed down a vicious monkey and had brought him around from an antisocial to a social attitude. Somehow this item, which was effectively illustrated, "clicked," and the descriptive word "tranquilize" stuck in our minds. This word caused us to wonder how this drug would affect a narcotic addict. When we first began to use it, our thoughts were that, if it would do a little tranquilizing here, it would prove worthwhile. We therefore tried it. The tablet size we used was 0.25 mg., and we were guided by the dosage suggestion on the label. We did not meet with much success. We accordingly increased the dose to four tablets, or a total of 1 mg. Returning to the cell block in about two hours, we thought we detected a more eased attitude on the part of our patients.

The next day, our given dose was 2 mg. per patient and, on returning in about two hours, we found that these patients, who had been yawning and beginning to jerk and retch a bit, were now comfortable. Some were dozing, and some were even sleeping.

After two or three more days, both Freund and McMahon asked what kind of new medicine was being given to the addicts in the narcotic detention block, for, whatever it was, the new drug was making their work of interrogation and cataloguing much easier. The prisoners were now calmer, less jumpy, and more responsive.

After due explanation we managed, with the help of these officers, to keep records concerning more than 300 temporarily detained drug-taking prisoners. In this way we discovered the following facts:

(1) Any drug addict or user who has become one because he has sought a thrill, or because of curiosity, can be tranquilized and sedated by the use of reserpine (Serpasil), and it is quite possible that a follow-up of any such case would reveal a complete warding off of the dreaded narcotic withdrawal sickness under this treatment.

(2) Furthermore, it seems quite possible that those who use narcotic drugs because of some painful ailment, such as ulcers or rheumatism, can be tranquilized and sedated by reserpine to such an extent that they may find it possible to give up habit-forming drugs and to get pain relief from a much less vicious source.

(3) Many of these drug addicts appear to intensify their pain psychologically by the use of habit-forming drugs. There is every reason to believe that reserpine can and will help to diminish this sort of psychic pain.

(4) As to the time element pertaining to the response to Serpasil, we found: the morphine addict responds in about one and one-half hours after oral administration; the heroin addict, in about two hours after oral administration; and the alcoholic and marihuana user, usually, in less than one hour. The parenteral form of reserpine was not used at any time. The age brackets were 18 to 30 for heroin addicts, most of whom were the nervous, jumpy, noisy type. They were mostly colored females. The age range of the morphine group was from 30 years upwards, white females predominating.

As we continued our investigation of Serpasil, we began to wonder if we were being carried away with undue enthusiasm. Thus when we discovered that Ciba Pharmaceutical Products would supply us with an undetectable placebo which looked and tasted exactly like Serpasil, we were more than happy to carry on the work we had started. When these placebos were received, we decided to deputize both of our narcotic police officers as our "interns" and, as such, we left with them an adequate supply of reserpine placebos with the suggestion that they give these tablets to their charges whenever they deemed necessary.

This they agreed to do, but they never could understand why it was that the tablets they gave out did not tranquilize and sedate in the same manner as did those dispensed by the doctor. Someday, perhaps, we may let them in on the secret but, in the meantime, it seems they believe that the doctor has a certain knack for handling medicine that is quite different from that of a policeman.

In conclusion, we again call your attention to these facts: (1) this experiment was carried out in a police station; (2) the experiment was tried on freshly arrested prisoners; (3) the daily time period of the experiment was limited to a few hours because the transfer of prisoners to other locations left us no opportunity for follow up; (4) our dosage began with two 1-mg. tablets and was repeated in four hours, if needed; (5) the dosage asserted itself within one and one-half to two hours after oral medication; (6) the morphine addict responded to reserpine more rapidly than did the heroin addict; (7) marihuana users were readily influenced by reserpine, as were the alcoholics, while the dose for both was smaller; and (8) last but not least, we believe there are certain possibilities offered by reserpine that warrants further investigation by other police departments, as well as by other organizations having to do with the narcotic problem, if only because the tranquilizing sedation brought about by this new drug apparently wards off the withdrawal sickness so feared by all addicts.

We all know that the manufacture, use, or possession of heroin is not permitted within the continental United States or its possessions, and this same regulation has been adopted by many other countries. We know that heroin has absolutely no place in medicine and is therefore not used by the healing profession. Furthermore, we know that the great source of contraband heroin supply is Red China. We also know that an addict fears the mental torture of going without his drug more than anything else on earth. The addict also hates and fears those mental problems that face him on the long road to recovery. These problems, he will tell you, are really what impel him to go back to the drug over and over again.

We also all know that an addict is the world's greatest liar. As a matter of fact, it is the only bit of defense mechanism to which he can and does lay claim. He does have his moments, however, when "everything is rosy," and it is during these periods that he will confide in one. One of his confidences will be his admission of fear pertaining to his mental well-being during and after withdrawal.

Should further study bring to light the fact that organized follow-up treatment confirms our experimental findings as regards reserpine, wherein we apparently erased the fearful mental aspects of narcotic withdrawal sickness from the picture, then we feel that this growing national plague, this known vicious contraband narcotic-laden Communistic invasion into the ranks of our American youth can be combated more readily. Surely this in itself should encourage further investigation.

Acknowledgment

My final word is to acknowledge the help of my friend Doctor William Braid White, who gave me valuable assistance in arrangement of the manuscript.

THE TRANQUILIZING EFFICACY OF RESERPINE IN DERMATOLOGICAL THERAPY

By Charles R. Rein and J. John Goodman

Department of Dermatology and Syphilology, New York University Post-Graduate Medical School; and the Skin and Cancer Unit of the New York University Hospital, New York, N.Y.

The many excellent reports presented in this Monograph have already established the efficacy of reserpine in the treatment of neuropsychiatric, neurological, and related clinical problems. In addition, there have been numerous publications attesting to the ability of this drug to alleviate free-floating anxieties without the concomitant soporific and sedative effects usually observed in using the barbiturates.

Serpasil represents a pure crystalline alkaloid of *Rauwolfia serpentina*, a small shrub indigenous to India. The roots of this plant had been used medicinally in Europe over 300 years ago for the treatment of anxiety states.[1] In 1933, its value as a hypotensive agent was reported by a group of Indian investigators.[2] Reserpine, thought to be the most important of the serpentine alkaloids, was first isolated in 1952 in Switzerland. Among the pharmacological effects noted was a quietude and reduction of emotional response.[3] In the Monograph on reserpine and other alkaloids of *Rauwolfia serpentina* published by the New York Academy of Sciences April 30, 1954,* many aspects of the clinical value of this drug were discussed. In addition to its value as an antihypertensive agent, Wilkins[4] reported on the increased sense of well-being produced and on the ability of the drug to decrease neurotic symptoms in patients; Hafkenschiel and Sellers,[5] in discussing the value of reserpine (Serpasil) as an antihypertensive drug, also remarked on the side effects of relaxation and sedation. Reserpine apparently does not have the marked soporific and narcotic effects of the barbiturates. According to Wilkins,[4] "Patients tell you that *Rauwolfia* or reserpine will make them sleepy, but will not put them to sleep." Harris,[6] in discussing the use of reserpine in geriatric hypertensives, also commented on the relaxing qualities of this drug. Kline,[7] in his discussion of the sedative qualities of *Rauwolfia* in neuropsychiatric patients, suggested that this drug be tried in other disorders, among which he included alcoholism, gastric ulcer, and atopic dermatitis. The tranquilizing qualities of reserpine in a number of patients with premenstrual tension were described by Greenblatt.[8]

In considering the pharmacological action of reserpine, Plummer and his associates[3] noted that the major effect was the production of relaxation and sedation in the unanesthetized animal. It was also noted that the electroencephalogram showed a normal pattern in contrast to the sleep pattern seen with the use of barbiturates. Consequently, these authors felt that, in contrast to the barbiturates, the main action of reserpine is a tranquilizing one, rather than a direct hypnotic action which may permit but does not cause sleep.

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* Annals of The New York Academy of Sciences 59(1): 1–140, based on a conference held by the Academy on February 5, 1954.

On administering reserpine to a dog, miosis, bradycardia, relaxation of the nictitating membrane, and augmentation of secretory and motor activity in the gastrointestinal tract were among other responses noted. Reserpine also caused a slowly developing drop in the mean arterial blood pressure. On the basis of pharmacological observations, it is believed that this drug acts on the central nervous system in the area of the hypothalamus. There appears to be an alteration of the sympathetic-parasympathetic balance by partial suppression of the sympathetic predominance. This change might well fit in with the observation of Hess,[9] who feels that sleep is a parasympathetic function caused by suspension of sympathetic activity in the hypothalamus. Therefore, reserpine, which probably also causes some suppression of the sympathetic activity in the hypothalamus, might easily be expected to produce relaxation and tranquilization.

Additional studies dealing with the mechanism of reserpine have been carried out by Himwich and Rinaldi,[10] who have reported as follows: "In rabbits tested in a special experimental setup providing recordings of electrical potential changes from the brain cortex and from the reticular formation in the brain stem, Serpasil consistently was found to stimulate the reticular formation while its action on other areas was inconsistent. Since the reticular formation is known to be directly involved in arousal and sleep phenomena, the action noted above helps to account for the fact that Serpasil does not produce sleep even though it has a tranquilizing or sedative action."

In studying the effects of reserpine on behavior and autonomic regulating mechanisms in the monkey, Schneider and Earl[11] summarized their findings as follows:

"(1) Reserpine (Serpasil) was given to a group of *Macaca mulatta* monkeys in varying doses and by different routes of administration. The effect on behavior, electroencephalograms, body temperature, systolic blood pressure, heart rate, respiratory rate, and pupillary diameter were studied.

"(2) Single intravenous doses of 0.5 to 1 mg./kg. and single oral doses of 50 mg. per kg. produce a state of quietude and unresponsiveness to extraneous stimuli, characterized by an essentially normal electroencephalogram, which distinguishes this state of tranquilization clearly from sleep induced by barbiturates.

"(3) Parallel to the changes in behavior, a drop in body temperature, an equivocal drop of blood pressure, a reduction of heart rate and respiratory rate were observed, whereas miosis and diarrhea, commonly seen in other species after Serpasil were not present.

"(4) The threshold dose for chronic daily oral administration in the monkeys was 2 to 3 mg./kg.

"(5) Increasing the dose by all routes of administration did not enhance the effects observed but tended to prolong them. Toxic manifestations were not encountered after Serpasil in doses up to 4 mg./kg. intravenously and 400 mg./kg. orally.

"(6) The results of this study are in agreement with the experimental findings in other species and in man, and further support the theory that the main point of attack of this drug is probably in the brain stem."

The following study[12] was undertaken to evaluate the tranquilizing and relaxing effects of Serpasil* in a selected group of 60 patients with various dermatoses in whom there was an uncontrollable urge to scratch, or in whom a tension or "nervous" factor contributed to the cutaneous disorder, as follows:

Diagnosis	No. of Patients
Atopic dermatitis	21
Neurodermatitis (*Lichen simplex chronicus*)	18
Anogenital pruritus	7
Dermatitis herpetiformis	6
Lichen planus	4
Neurotic excoriations	2
Chronic urticaria	2
Total	60

The dosage was 0.25 mg. four times daily for one month. Patients were re-examined at weekly intervals and questioned as to subjective sensations. Blood pressure and pulse were recorded each time. It was felt that in evaluating such a highly suggestible group of patients, some irrelevant questions concerning the drug, such as symptoms relative to joint pains, blurring vision, and the like, should be inserted among the routine questioning in order that the study be as objective as possible.

In analyzing the results, it was noted that most patients experienced moderate drowsiness and fatigue, starting usually from the second to the fourth day after onset of therapy. These symptoms gradually subsided during the second week. In general, there appeared to be a considerable variation in response to dosage. While it was felt that the clinical response to Serpasil could be altered by varying the dose, a constant dosage was maintained for simplicity and standardization of this study.

Forty of the 60 patients experienced definite relaxation, tranquilization, sedation, and lessening of inner tension. There was no significant blood pressure or pulse change in this essentially normotensive group of patients.

Six additional patients with marked palmar hyperhidrosis were placed on reserpine therapy, 0.25 mg. four times a day. Within two weeks, there was a decided reduction in the degree of hyperhidrosis. It was of special interest that these patients had failed to respond to previously employed local and oral therapy. It is reasonable to suppose that reserpine would be of benefit in those patients with palmar hyperhidrosis in whom exacerbations were associated with emotional factors.

Side reactions, none of which was considered of major importance, were encountered as follows: nasal congestion, 24; increased appetite, 13; dreams, 8; and nocturia, 8.

Therapy was discontinued in five patients during the first week because of marked fatigue, drowsiness, and weakness; in two patients with an asthmatic background because of moderate dyspnea; in two patients who developed nausea, and in one patient because of a moderate depression. All of these side effects disappeared a short time following cessation of therapy. These 10 patients are not included in the total of 60 evaluated.

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* Provided by the Research Department, Ciba Pharmaceutical Products, Inc., Summit, N. J.

Nasal congestion, representing the highest incidence of side effects, responded promptly to oral antihistaminic therapy and, for the most part, appeared to subside with time. Many patients with increased appetites noted a corresponding weight gain. An interesting side effect was nocturia, where it previously had not existed. This fact might possibly be explained by an increased appetite and, therefore, corresponding increased fluid intake.

Thirty of the patients in this series were arbitrarily maintained a month or longer on placebo therapy after one month on reserpine without being notified of a change of medication, so that even further control could be exercised. Of these, 22 stated that there was diminution in the degree of relaxation or sedation. Also, those patients with side effects, while on the active preparation, noted that these effects disappeared soon after placebo therapy was instituted. The same objective type of interrogation as with the active drug was used. Many patients initially volunteered that they felt the pills had lost their effect. One patient, however, stated that he discontinued taking the placebo tablets after two weeks of therapy because of continued marked fatigue and nasal congestion, which had occurred initially with the administration of the active drug. In general, it was noted that the effects of reserpine wore off by the end of two weeks after it had been discontinued. In seven patients, however, there appeared to be a reserpine effect extending beyond two weeks of placebo therapy.

Tranquilizing drugs are of great value to the dermatologist in the management of patients with various widespread pruritic dermatoses. A concomitant improvement of the skin condition may be expected when tranquility and better sleeping habits are obtained. One should not expect, however, to cure a skin disease as a direct result of using such a drug, any more than one would expect to achieve spectacular improvement with the administration of barbiturates alone. In "The Schoch Letter," in the November 1954 issue of *Current News in Dermatology and Syphilology*, Lenahan[13] reports on the poor results he obtained with reserpine. He treated 26 patients, including seborrheic dermatitis, atopic dermatitis, psoriasis, neurodermatitis, postzoster pain, and hyperhidrosis. He believes that this drug did not contribute to any improvement in these patients and that they did not feel as tranquil as similar patients taking one half of a grain of phenobarbital three times daily. He is of the opinion that "this small group of patients cannot provide an accurate picture of the value of Serpasil, but I believe it is large enough to demonstrate the absence of any spectacular results."

In the same "Schoch Letter," Kesten[14] comments on the tranquilizing effect of *Rauwolfia* alkaloids in widespread pruritic dermatoses. She found reserpine, 0.25 mg. four times a day, to be extremely helpful in the management of highly "nervous" patients, with or without hypertension, who have a long standing uncontrollable urge to scratch. Patients with chronic allergic eczema, chronic dermatitis of unknown origin, or what might be termed cholinergic itching, have become more tranquil when on the drug. She also achieved excellent results in a few patients with dyshidrosis, axillary dermatitis, or in those made worse by perspiration. Two patients stimulated by ACTH were less restless and slept better. Three patients with exacerbations of neurodermatitis disseminata remarkably improved, and two patients with severe anogenital pruritus were benefited. Patients became more tranquil within 24 to 48 hours.

The editors[15] of "The Schoch Letter" believe that the alkaloids of *Rauwolfia* need be administered from one to two weeks to obtain their full tranquilizing effect. Their single most dramatic observation was on an agitated, treated patient with general paresis. He became docile and completely manageable. They state, "If these tranquilizing drugs prove to be safe for prolonged administration, life will become more simplified for many of us. We ardently hope that at the meeting next month of the American Academy of Dermatology and Syphilology, we can add to our definitive knowledge of these tranquilizing drugs." Many of the dermatologists who attended that meeting had used reserpine, and the majority attested to its excellent tranquilizing efficacy.

Our continued experience in additional series of more than 300 dermatological patients are similar to those observed in the original 60 patients reported above.

In a recent publication, Fries[16] described the development of psychiatric complications in hypertensive patients treated with large doses of reserpine for long periods. Five cases of mental depression were noted after several months of continued treatment with reserpine in dosage varying from 1.0 to 2.0 mg. a day in four and 0.25 mg. a day in one of the cases. The author believes that maintenance doses of this agent should be kept below 0.25 mg. a day, to minimize the development of this syndrome.

One individual under our observation also developed this psychiatric complication while taking reserpine.

Case Report

C. R., a 32-year-old white male, took 1 mg. of this drug per day in four divided doses, beginning in April 1954, for a period of one month. In addition to its tranquilizing effect, he noted a transitory nasal congestion. Reserpine was again resumed, because of a feeling of tension during the latter part of May, in daily doses from 1 to 3 mg., and was maintained for five months. In July, he became moderately depressed and lost all self-confidence. He also lost his usual enthusiasm for work and became excessively introspective. He wanted to remain at home and was incapable of enjoying many of the things that had formerly afforded him considerable pleasure. His ability to concentrate became retarded, and he was unable to make any important decisions by himself. His appetite remained good during the entire period of mental depression. Temporary improvement was afforded by shock therapy, but complete recovery was noted within a few weeks after reserpine was discontinued.

Summary

(1) Sixty patients with various dermatoses were placed on reserpine for one month. Each patient took 1 mg. daily in divided doses. Thirty of these

patients were further maintained for an additional month on placebo therapy. Patients were re-examined at weekly intervals, blood pressure and pulse also being recorded.

(2) Forty of the 60 patients experienced definite relaxation, tranquilization, or slept better.

(3) Side effects included nasal congestion, increased appetite, depression, dreams, nocturia, dyspnea, weakness, and nausea. These necessitated discontinuation of therapy in 10 patients, which are not included in the total of 60 evaluated.

(4) Of the 30 patients maintained on placebo therapy, it was readily discernible in 22 that there was a diminution in the degree of relaxation or sedation and a lessening of the side effects.

(5) There was no significant blood pressure-pulse change noted in this essentially normotensive group.

(6) Six patients with hyperhidrosis experienced moderate improvement while taking reserpine.

(7) Reserpine is another excellent drug to be added to the armamentarium of the dermatologist when in need of a tranquilizing and relaxing agent.

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PREOPERATIVE, PEROPERATIVE, AND POSTOPERATIVE SEDATION WITH RESERPINE*

By C. R. Stephen, M. Bourgeois-Gavardin, and R. C. Martin
Division of Anesthesia, Duke University Hospital and School of Medicine, Durham, N.C.

Within the last year, reserpine has received clinical appraisal as a drug which produces a quieting and tranquilizing effect in the human,[1] and is also useful in providing a moderate reduction of blood pressure in hypertensive patients.[2] Its application in medicine has been directed primarily toward the treatment of certain psychiatric disorders and as an ancillary compound in the therapy of hypertension. Pharmacological investigations have indicated that the probable site of action of this drug is in the hypothalamus.[3]

While knowledge regarding reserpine has been increasing, considerable attention has been focused also on the therapeutic applications of a phenothiazine derivative, chlorpromazine. This drug has been recommended as an antiemetic,[4] as an aid to the production of hypothermia,[5] as a potentiator of sedative and narcotic drugs,[6] and for its calming influence in the treatment of certain psychiatric diseases.[7] It is known also to produce hypotension in a certain percentage of patients.[8] One of its principal sites of action is believed to be in the hypothalamus.[9]

Here, then, are two compounds, dissimilar in chemical configuration, which are believed to exert their principal actions in the same part of the central nervous system. They appear to have certain properties in common, namely: (1) a calming and sedative influence on the central nervous system; (2) the production of a moderate hypotension as a result of peripheral vasodilatation;[10] and (3) a nonspecific effect on certain psychiatric diseases. Yet their clinical applications in medicine have been somewhat divergent, except in the field of psychiatry.

In an effort to find out more concerning the pharmacology of these drugs, their action as sedative compounds before, during, and after operation has been compared in the human. It has also been possible to determine their influence on the cardiovascular system, both in the animal and the human. The studies have been carried out in similar groups of surgical patients and in dogs, utilizing the same experimental methods for both compounds.

Preanesthetic Sedation

A group of 87 patients received reserpine,† 0.5, 1.0, 2.0, or 5.0 mg., intravenously or intramuscularly, approximately one hour before induction of anesthesia (TABLE 1). These patients were watched closely and interrogated frequently. None of the patients became drowsy or lost contact with his immediate environment. Those who were apprehensive remained apprehensive until the induction of anesthesia. One patient developed a marked flush-

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* Supported by a grant from Ciba Pharmaceutical Products, Inc., Summit, N. J.

† We are indebted to Ciba Pharmaceutical Products, Inc., Summit, N. J., for generous supplies of reserpine Serpasil).

TABLE 1

DOSAGE OF RESERPINE ADMINISTERED TO PATIENTS

Reserpine	Patients
0.5 mg. (I. M.)	9
0.5 mg. (I. V.)	2
1.0 mg. (I. M.)	19
1.0 mg. (I. V.)	16
2.0 mg. (I. M.)	2
2.0 mg. (I. V.)	8
5.0 mg. (I. M.)	3
5.0 mg. (I. V.)	28

TABLE 2

DOSAGE OF CHLORPROMAZINE ADMINISTERED TO PATIENTS

Chlorpromazine	Patients
25 mg. (I. V.)	45
25 mg. (I. M.)	57
35 mg. (I. M.)	64
50 mg. (I. M.)	34

ing of the face and upper trunk in a cloak distribution, 30 minutes after receiving 2.0 mg. intravenously. No other unusual side effects were seen.

Two hundred patients were given 25, 35, or 50 mg. of chlorpromazine* intramuscularly 30 to 45 minutes prior to surgery (TABLE 2). About 75 per cent of these patients became drowsy or indifferent within 30 minutes of the time of administration. Fear and apprehension diminished, and the patients gave the impression of being "disconnected" from their surroundings, although questions would be answered in a rational manner. The cerebral sedative effect appeared to be more pronounced with chlorpromazine than with reserpine in the doses given. In those patients who were given spinal anesthesia, the more pronounced sedative effects of chlorpromazine continued to manifest themselves during the course of operation.

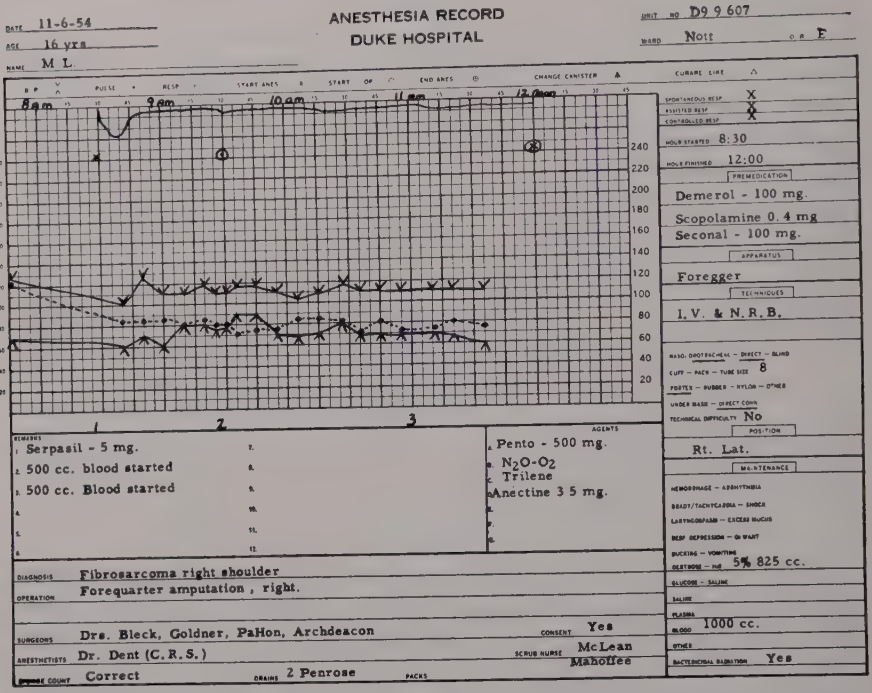
Effect During Anesthesia and Surgery

Those patients who received reserpine preoperatively appeared to require quantities of anesthetic drugs similar to those of a control group. Clinically, reserpine did not potentiate the effect of barbiturates, analgesics, or narcotics.

The experience with patients who received chlorpromazine was in direct contrast to those receiving reserpine or no drug at all. In the majority of patients, chlorpromazine reduced perceptibly the total quantity of anesthetic drugs required. This was noted particularly in patients who came to surgery more than once, and who, therefore, could serve as their own "control."[8]

Inasmuch as blood pressures and pulse rates were recorded frequently dur-

* We are indebted to Smith, Kline and French, Ltd., Philadelphia, Pa., for generous supplies of chlorpromazine (Thorazine).



DATE 11-6-54
AGE 16 yrs
NAME M L.

ANESTHESIA RECORD
DUKE HOSPITAL

UNIT NO D9 9 607
WARD Nott O R E

SPONTANEOUS RESP X
ASSISTED RESP X
CONTROLLED RESP X
HOUR STARTED 8:30
HOUR FINISHED 12:00

PREMEDICATION
Demerol - 100 mg.
Scopolamine 0. 4 mg
Seconal - 100 mg.

APPARATUS
Foregger

TECHNIQUES
I. V. & N. R. B.

NASO, OROTRACHEAL — DIRECT — BLIND
CUFF — PACK — TUBE SIZE 8
PORTEX — RUBBER — NYLON — OTHER
UNDER MASK — DIRECT CONN
TECHNICAL DIFFICULTY No

POSITION
Rt. Lat.

MAINTENANCE
HEMORRHAGE — ARRHYTHMIA
BRADY/TACHYCARDIA — SHOCK
LARYNGOSPASM — EXCESS MUCUS
RESP DEPRESSION — O₂ WANT
BUCKING — VOMITING
DEXTROSE — H₂O 5% 825 cc.
GLUCOSE — SALINE
SALINE
PLASMA
BLOOD 1000 cc.
OTHER
BACTERICIDAL RADIATION Yes

REMARKS
1. Serpasil - 5 mg.
2. 500 cc. blood started
3. 500 cc. Blood started
4.
5.
6.
7.
8.
9.
10.
11.
12.

AGENTS
a. Pento - 500 mg.
b. N_2O-O_2
c. Trilene
d. Anectine 3 5 mg.
e.
f.
g.

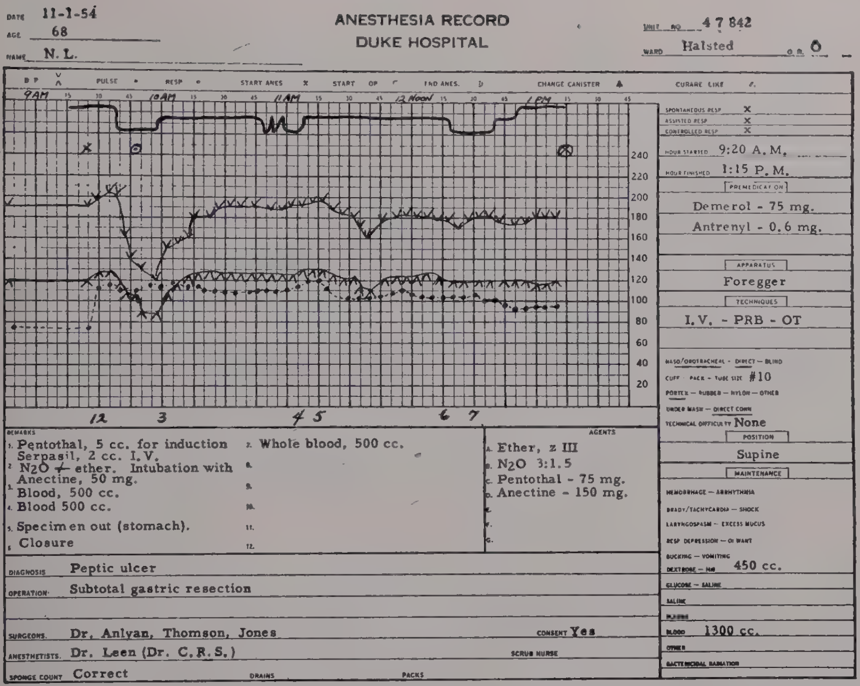
DIAGNOSIS Fibrosarcoma right shoulder
OPERATION Forequarter amputation , right.
SURGEONS Drs. Bleck, Goldner, PaHon, Archdeacon
CONSENT Yes
ANESTHETISTS Dr. Dent (C. R. S.)
SCRUB NURSE McLean Mahoffee
[illegible] COUNT Correct
DRAINS 2 Penrose
PACKS

CHART 1. Reserpine, 5 mg. intravenously, produced no remarkable change in blood pressure or pulse rate.

ing operation, the effects of the two drugs on these manifestations of cardiovascular function could be assessed. In the normotensive patient, reserpine showed little tendency to alter the blood pressure or pulse rate (CHART 1). In some hypertensive patients (CHART 2), reserpine exerted no marked effect whereas, in others, a definite tendency towards hypotension was noted (CHART 3). In most patients with elevated blood pressure preoperatively, a gradual and not alarming reduction in pressure occurred (CHART 4). It is believed that reserpine, in doses up to 5 mg. intravenously or intramuscularly, can be given to most surgical patients without fear of the development of profound hypotension. When hypotension does appear to be of concern, the patient will respond to vasopressor drugs in a satisfactory manner.

A significant reduction in blood pressure (40 mm. Hg or more systolic) occurred in 12 per cent of the patients to whom chlorpromazine was administered.[8] CHART 5 is an example of hypotension developing in a normotensive patient. This patient did not respond as anticipated to the injection of the vasopressor desoxyephedrin. Rapid reductions in pressure occurred in hypertensive patients also (CHART 6). These patients also did not respond adequately to vasopressor drugs.

It is the belief that hypotension following the injection of chlorpromazine is more frequent, of more rapid onset, and more profound than that seen after reserpine administration. The fact that patients receiving chlorpromazine are resistant to the action of vasopressor drugs would tend to suggest that the



DATE 11-1-54
AGE 68
NAME N. L.

ANESTHESIA RECORD
DUKE HOSPITAL

UNIT NO 4 7 842
WARD Halsted O.R. 6

CURARE LIKE
SPONTANEOUS RESP X
ASSISTED RESP X
CONTROLLED RESP X
HOUR STARTED 9:20 A.M.
HOUR FINISHED 1:15 P.M.

PREMEDICATION
Demerol - 75 mg.
Antrenyl - 0.6 mg.

APPARATUS
Foregger

TECHNIQUES
I.V. - PRB - OT

NASO/OROTRACHEAL - DIRECT - BLIND
CUFF - PACK - TUBE SIZE #10
PORTEX - RUBBER - NYLON - OTHER
UNDER MASK - DIRECT CONN
TECHNICAL DIFFICULTY None

POSITION
Supine

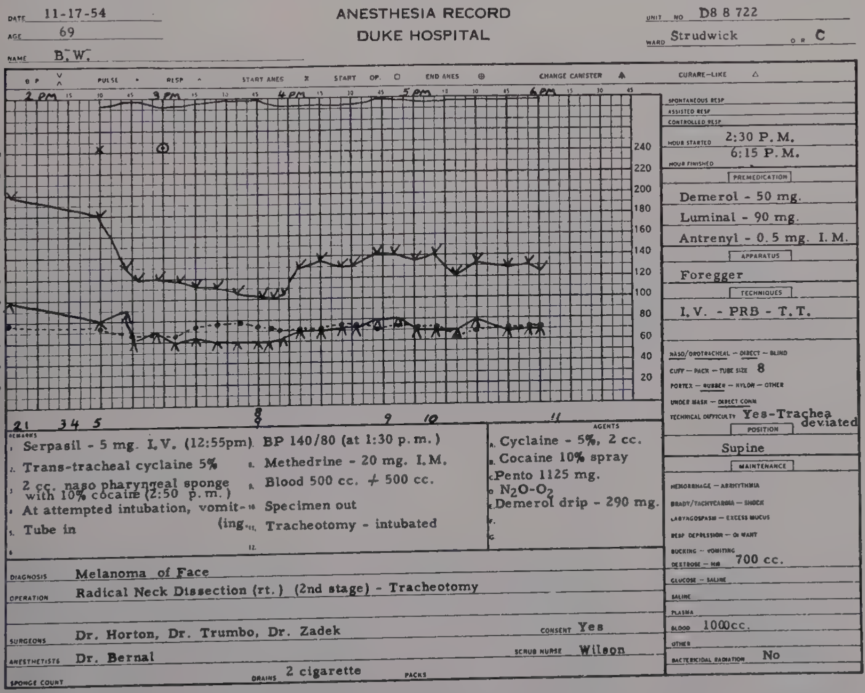
MAINTENANCE
HEMORRHAGE - ARRHYTHMIA
BRADY/TACHYCARDIA - SHOCK
LARYNGOSPASM - EXCESS MUCUS
RESP DEPRESSION - O2 WANT
BUCKING - VOMITING
DEXTROSE - NS 450 cc.
GLUCOSE - SALINE
SALINE
PLASMA
BLOOD 1300 cc.
OTHER
BACTERICIDAL RADIATION

REMARKS
1. Pentothal, 5 cc. for induction Serpasil, 2 cc. I.V.
2. N2O + ether. Intubation with Anectine, 50 mg.
3. Blood, 500 cc.
4. Blood 500 cc.
5. Specimen out (stomach).
6. Closure
7. Whole blood, 500 cc.
8.
9.
10.
11.
12.

AGENTS
A. Ether, z III
B. N_2O 3:1.5
C. Pentothal - 75 mg.
D. Anectine - 150 mg.
E.
F.
G.

DIAGNOSIS Peptic ulcer
OPERATION Subtotal gastric resection
SURGEONS Dr. Anlyan, Thomson, Jones CONSENT Yes
ANESTHETISTS Dr. Leen (Dr. C.R.S.) SCRUB NURSE
SPONGE COUNT Correct DRAINS PACKS

CHART 2. Reserpine, 2 mg. intravenously, showed no effect on blood pressure or pulse rate. Hypotension shortly after induction believed due to vasodilatation associated with high ethyl ether blood concentration.



DATE 11-17-54
AGE 69
NAME B. W.

ANESTHESIA RECORD
DUKE HOSPITAL

UNIT NO D8 8 722
WARD Strudwick O.R. C

CURARE-LIKE △
SPONTANEOUS RESP
ASSISTED RESP
CONTROLLED RESP
HOUR STARTED 2:30 P.M.
HOUR FINISHED 6:15 P.M.

PREMEDICATION
Demerol - 50 mg.
Luminal - 90 mg.
Antrenyl - 0.5 mg. I.M.

APPARATUS
Foregger

TECHNIQUES
I.V. - PRB - T.T.

NASO/OROTRACHEAL - DIRECT - BLIND
CUFF - PACK - TUBE SIZE 8
PORTEX - RUBBER - NYLON - OTHER
UNDER MASK - DIRECT CONN
TECHNICAL DIFFICULTY Yes-Trachea deviated

POSITION
Supine

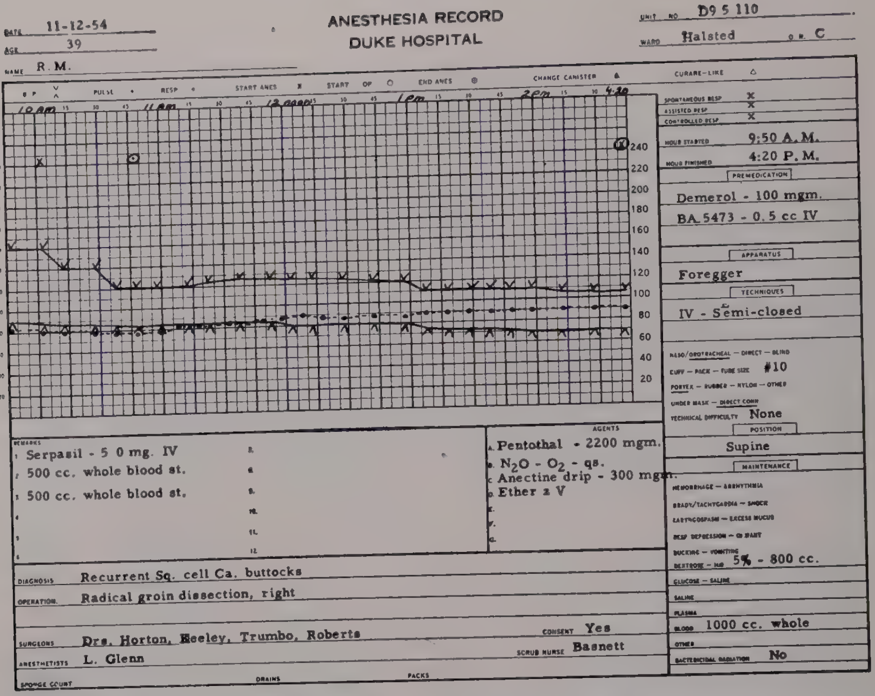
MAINTENANCE
HEMORRHAGE - ARRHYTHMIA
BRADY/TACHYCARDIA - SHOCK
LARYNGOSPASM - EXCESS MUCUS
RESP DEPRESSION - O2 WANT
BUCKING - VOMITING
DEXTROSE - NS 700 cc.
GLUCOSE - SALINE
SALINE
PLASMA
BLOOD 1000cc.
OTHER
BACTERICIDAL RADIATION No

REMARKS
1. Serpasil - 5 mg. I.V. (12:55pm).
2. Trans-tracheal cyclaine 5%
3. 2 cc. naso pharyngeal sponge with 10% cocaine (2:50 p.m.)
4. At attempted intubation, vomiting
5. Tube in
6.
7. BP 140/80 (at 1:30 p.m.)
8. Methedrine - 20 mg. I.M.
9. Blood 500 cc. + 500 cc.
10. Specimen out
11. Tracheotomy - intubated
12.

AGENTS
A. Cyclaine - 5%, 2 cc.
B. Cocaine 10% spray
C. Pento 1125 mg.
D. N_2O-O_2
E. Demerol drip - 290 mg.
F.
G.

DIAGNOSIS Melanoma of Face
OPERATION Radical Neck Dissection (rt.) (2nd stage) - Tracheotomy
SURGEONS Dr. Horton, Dr. Trumbo, Dr. Zadek CONSENT Yes
ANESTHETISTS Dr. Bernal SCRUB NURSE Wilson
SPONGE COUNT DRAINS 2 cigarette PACKS

CHART 3. Reserpine, associated with anesthesia, produced moderate hypotension (200/100 to 100/60). Fall in blood pressure responded adequately to vasopressor, desoxyephedrin.



ANESTHESIA RECORD
DUKE HOSPITAL

DATE 11-12-54
AGE 39
NAME R. M.
UNIT NO. D9 5 110
WARD Halsted
O. R. C

CURARE-LIKE △
SPONTANEOUS RESP ✕
ASSISTED RESP ✕
CONTROLLED RESP ✕
HOUR STARTED 9:50 A. M.
HOUR FINISHED 4:20 P. M.

PREMEDICATION
Demerol - 100 mgm.
BA 5473 - 0.5 cc IV

APPARATUS
Foregger

TECHNIQUES
IV - Semi-closed

NASO/ORO TRACHEAL — DIRECT — BLIND
CUFF — PACK — TUBE SIZE #10
PORTEX — RUBBER — NYLON — OTHER
UNDER MASK — DIRECT CONN
TECHNICAL DIFFICULTY None

POSITION
Supine

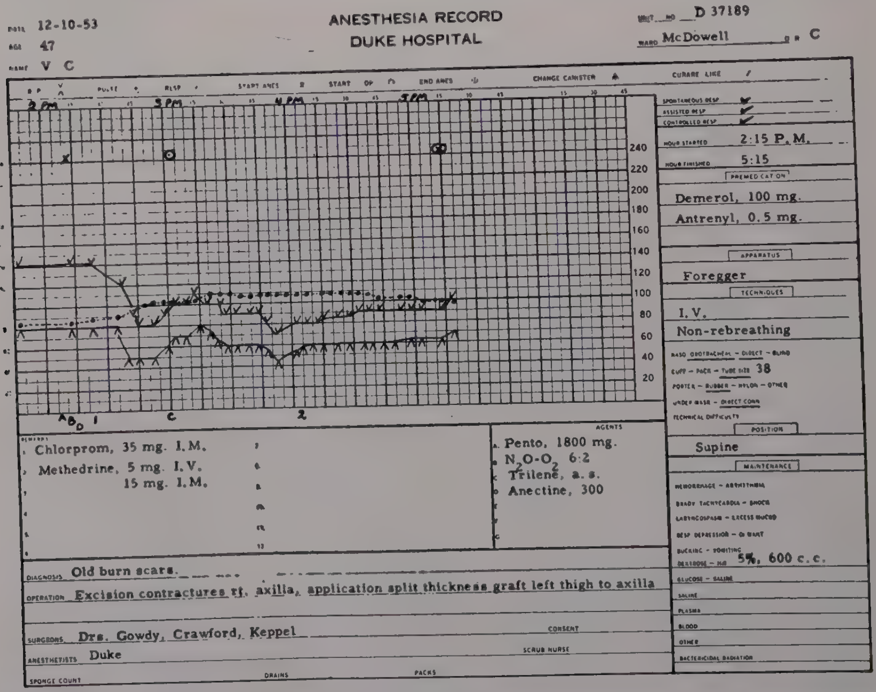
MAINTENANCE
HEMORRHAGE — ARRHYTHMIA
BRADY/TACHYCARDIA — SHOCK
LARYNGOSPASM — EXCESS MUCUS
RESP DEPRESSION — CO₂ WANT
BUCKING — VOMITING
DEXTROSE — H₂O 5% - 800 cc.
GLUCOSE — SALINE
SALINE
PLASMA
BLOOD 1000 cc. whole
OTHER
BACTERICIDAL RADIATION No

REMARKS
1. Serpasil - 5 0 mg. IV
2. 500 cc. whole blood st.
3. 500 cc. whole blood st.

AGENTS
A. Pentothal - 2200 mgm.
B. N₂O - O₂ - qs.
C. Anectine drip - 300 mgm.
D. Ether ✕ V

DIAGNOSIS Recurrent Sq. cell Ca. buttocks
OPERATION Radical groin dissection, right
SURGEONS Drs. Horton, Heeley, Trumbo, Roberts
CONSENT Yes
ANESTHETISTS L. Glenn
SCRUB NURSE Basnett
SPONGE COUNT
DRAINS
PACKS

CHART 4. Following reserpine, 5 mg. intravenously, gradual reduction in blood pressure occurred, associated with no change in pulse rate.



ANESTHESIA RECORD
DUKE HOSPITAL

DATE 12-10-53
AGE 47
NAME V C
UNIT NO. D 37189
WARD McDowell
O. R. C

CURARE LIKE /
SPONTANEOUS RESP ✓
ASSISTED RESP ✓
CONTROLLED RESP ✓
HOUR STARTED 2:15 P. M.
HOUR FINISHED 5:15

PREMEDICATION
Demerol, 100 mg.
Antrenyl, 0.5 mg.

APPARATUS
Foregger

TECHNIQUES
I. V.
Non-rebreathing

NASO OROTRACHEAL - DIRECT - BLIND
CUFF - PACK - TUBE SIZE 38
PORTEX - RUBBER - NYLON - OTHER
UNDER MASK - DIRECT CONN
TECHNICAL DIFFICULTY

POSITION
Supine

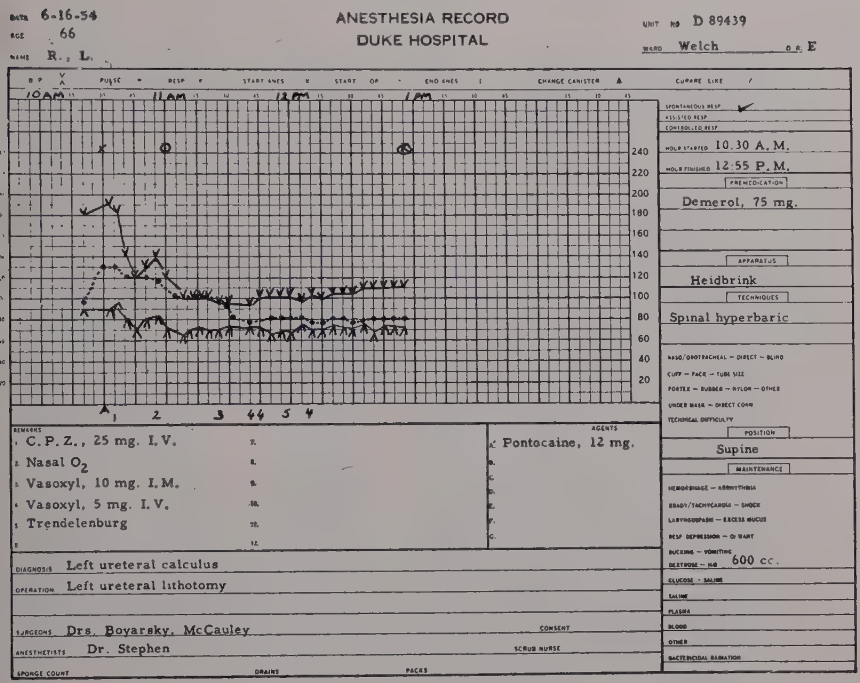
MAINTENANCE
HEMORRHAGE - ARRHYTHMIA
BRADY TACHYCARDIA - SHOCK
LARYNGOSPASM - EXCESS MUCUS
RESP DEPRESSION - O₂ WANT
BUCKING - VOMITING
DEXTROSE - H₂O 5%, 600 c. c.
GLUCOSE - SALINE
SALINE
PLASMA
BLOOD
OTHER
BACTERICIDAL RADIATION

REMARKS
1. Chlorprom, 35 mg. I. M.
2. Methedrine, 5 mg. I. V.
15 mg. I. M.

AGENTS
A. Pento, 1800 mg.
B. N₂O-O₂ 6:2
C. Trilene, a. s.
D. Anectine, 300

DIAGNOSIS Old burn scars.
OPERATION Excision contractures rt. axilla, application split thickness graft left thigh to axilla
SURGEONS Drs. Gowdy, Crawford, Keppel
CONSENT
ANESTHETISTS Duke
SCRUB NURSE
SPONGE COUNT
DRAINS
PACKS

CHART 5. Reduction of systolic blood pressure 60 mm. Hg following chlorpromazine, 35 mg. intramuscularly. N. B. lack of response to desoxyephedrin.



DATE 6-16-54
AGE 66
NAME R., L.

ANESTHESIA RECORD
DUKE HOSPITAL

UNIT NO D 89439
WARD Welch O.R. E

SPONTANEOUS RESP ✓
ASSISTED RESP
CONTROLLED RESP
HOUR STARTED 10.30 A.M.
HOUR FINISHED 12:55 P.M.

PREMEDICATION
Demerol, 75 mg.

APPARATUS
Heidbrink

TECHNIQUES
Spinal hyperbaric

NASO/OROTRACHEAL — DIRECT — BLIND
CUFF — PACK — TUBE SIZE
PORTEX — RUBBER — NYLON — OTHER
UNDER MASK — DIRECT CONN
TECHNICAL DIFFICULTY

POSITION
Supine

MAINTENANCE
HEMORRHAGE — ARRHYTHMIA
BRADY/TACHYCARDIA — SHOCK
LARYNGOSPASM — EXCESS MUCUS
RESP DEPRESSION — O₂ WANT
BUCKING — VOMITING
DEXTROSE — H₂O 600 cc.
GLUCOSE - SALINE
SALINE
PLASMA
BLOOD
OTHER
BACTERICIDAL RADIATION

REMARKS
1 C.P.Z., 25 mg. I.V.
2 Nasal O_2
3 Vasoxyl, 10 mg. I.M.
4 Vasoxyl, 5 mg. I.V.
5 Trendelenburg

AGENTS
A Pontocaine, 12 mg.

DIAGNOSIS Left ureteral calculus
OPERATION Left ureteral lithotomy
SURGEONS Drs. Boyarsky, McCauley
ANESTHETISTS Dr. Stephen
CONSENT
SCRUB NURSE
SPONGE COUNT
DRAINS
PACKS

CHART 6. Reduction in blood pressure from 180/90 to 100/70 following chlorpromazine, 25 mg. intravenously. N. B. lack of response to methoxamine on four occasions.

action of reserpine and the phenothiazine derivative are not alike in respect to their influence on blood pressure.

Animal Experiments

In an attempt to clarify this situation regarding cardiovascular function, certain experiments were performed in dogs. In the reserpine experiments, 10 dogs were given the drug intravenously in a dosage of 1 to 2 mg. per kilogram about two hours prior to actually commencing the study. This time interval was allowed in order to have a maximal drug effect. In the dogs

TABLE 3

TYPICAL BLOOD PRESSURE RESPONSES IN DOGS TO VASOPRESSOR DRUGS INTRAVENOUSLY FOLLOWING RESERPINE AND CHLORPROMAZINE

	Reserpine 1.0 mg./kilo	Chlorpromazine 1.5 mg./kilo
Base line	84/70	80/60
Ephedrin, 0.5 mg./K.	224/175	80/60
Desoxyephedrin, 0.2 mg./K.	132/84	80/60
Methoxamine, 0.2 mg./K.	154/105	84/60
Epinephrin, 0.005 mg./K.	182/147	100/70
Levoarteronal, 0.5 mg./K.	175/105	110/80

Increase in blood pressure following reserpine comparable to control values.

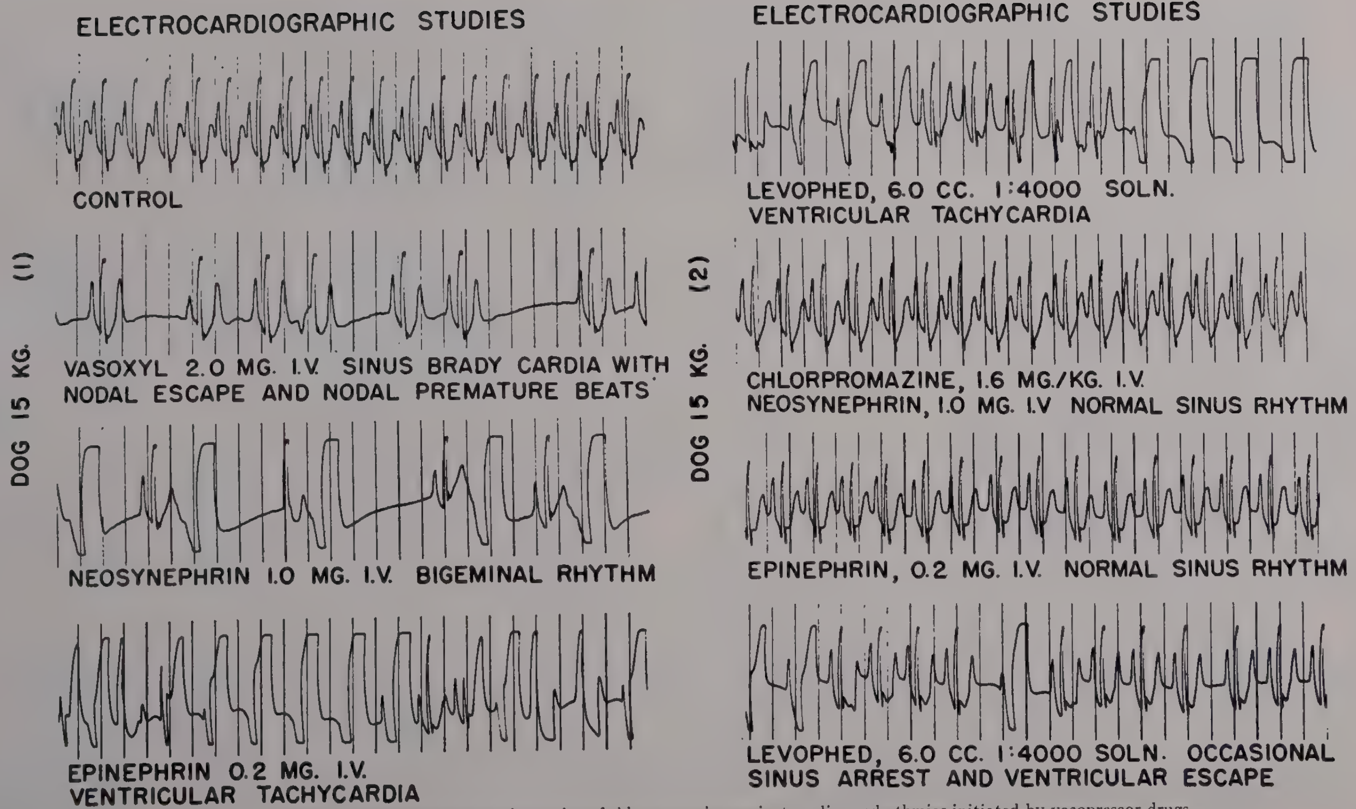


Chart 7. To show, in the dog, the protective action of chlorpromazine against cardiac arrhythmias initiated by vasopressor drugs.

receiving chlorpromazine, eight in number, the drug was administered at intervals during the course of the experiment. Under pentobarbital or pentothal sodium anesthesia, a femoral artery cutdown was done to record arterial pressure directly, and a femoral vein cutdown was completed for injection of drugs. Respirations were recorded by means of a pneumograph and Lead 2 of the

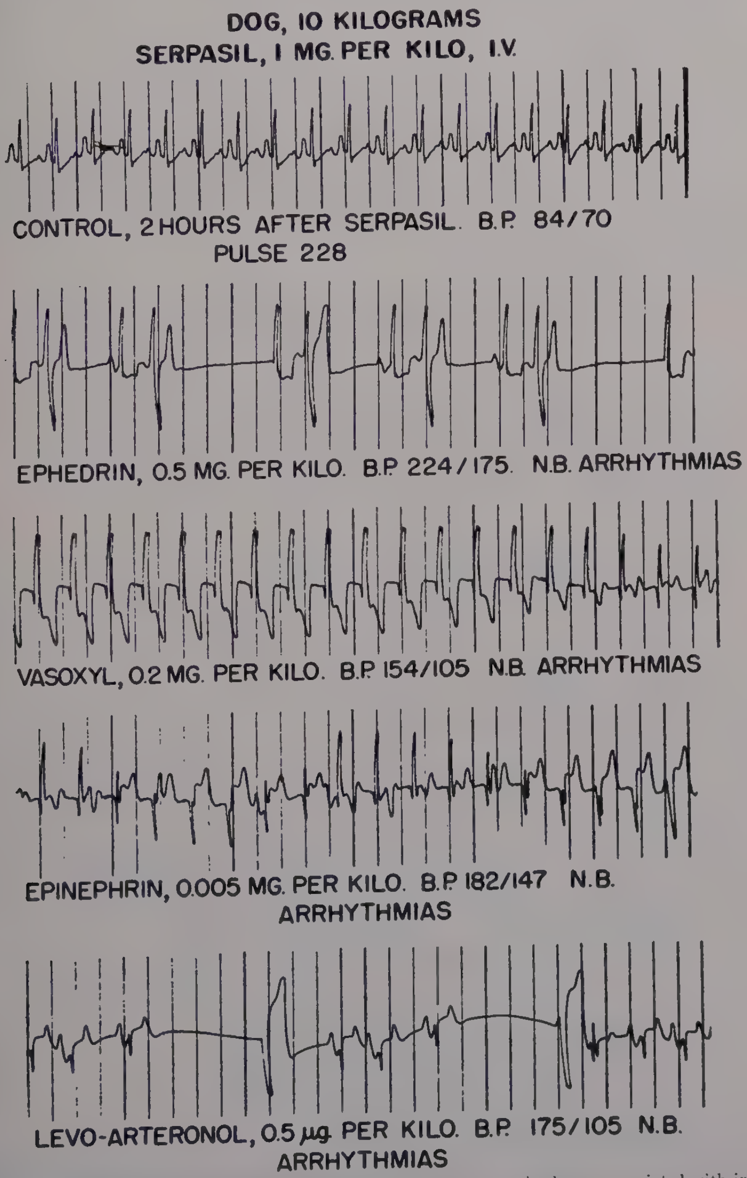

DOG, 10 KILOGRAMS
SERPASIL, 1 MG. PER KILO, I.V.
CONTROL, 2 HOURS AFTER SERPASIL. B.P. 84/70
PULSE 228
EPHEDRIN, 0.5 MG. PER KILO. B.P. 224/175. N.B. ARRHYTHMIAS
VASOXYL, 0.2 MG. PER KILO. B.P. 154/105 N.B. ARRHYTHMIAS
EPINEPHRIN, 0.005 MG. PER KILO. B.P. 182/147 N.B. ARRHYTHMIAS
LEVO-ARTERONOL, 0.5 µg. PER KILO. B.P. 175/105 N.B. ARRHYTHMIAS

CHART 8. To show, in the dog, that reserpine does not prevent arrhythmias associated with injection of sympathomimetic amines.

electrocardiogram was obtained continually. All records were made using an eight channel Grass electroencephalographic recorder, with the help of Statham strain gauges and balance demodulators.

The difference in the blood pressure responses to vasopressor drugs following reserpine and chlorpromazine is illustrated in TABLE 3. Chlorpromazine has a rather marked blocking effect, whereas elevations in blood pressure are not inhibited by reserpine.

Further evidence of a difference in action of the drugs can be obtained by comparing electrocardiographic changes associated with administration of sympathomimetic amines. CHART 7, tracings 2, 3, 4, and 5, show the types of arrhythmias which may follow vasopressor drugs intravenously. In the last three tracings can be seen the partial to complete protection afforded by chlorpromazine, 1.6 mg. per kilogram. In contrast to this, it is observed in CHART 8 that reserpine, in a dosage of 1 mg. per kilogram, does not prevent the development of arrhythmias.

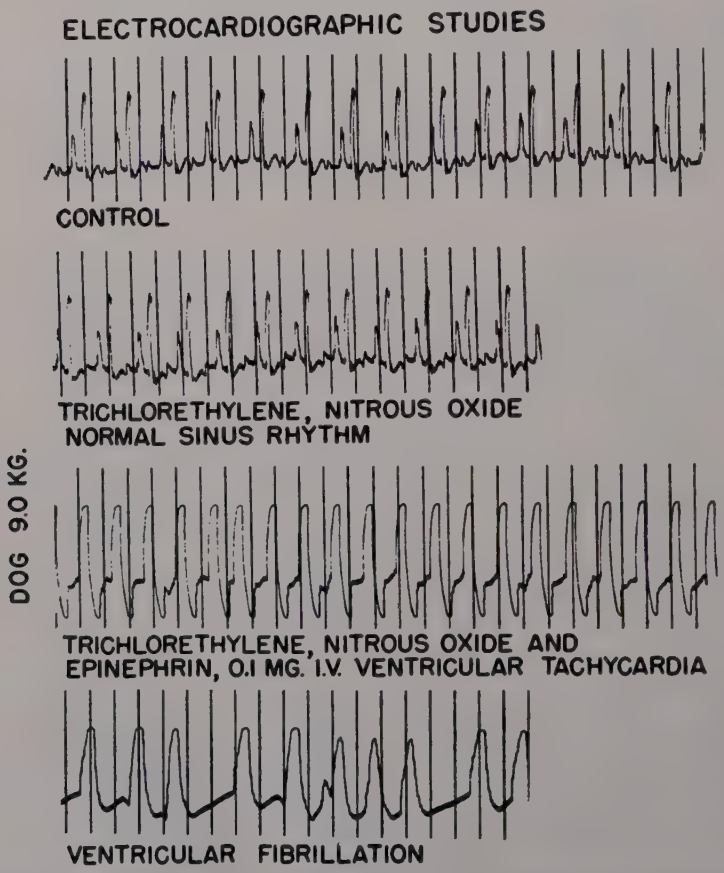


CHART 9. To show, in the dog, fatal ventricular arrhythmias associated with trichlorethylene-epinephrin combinations.

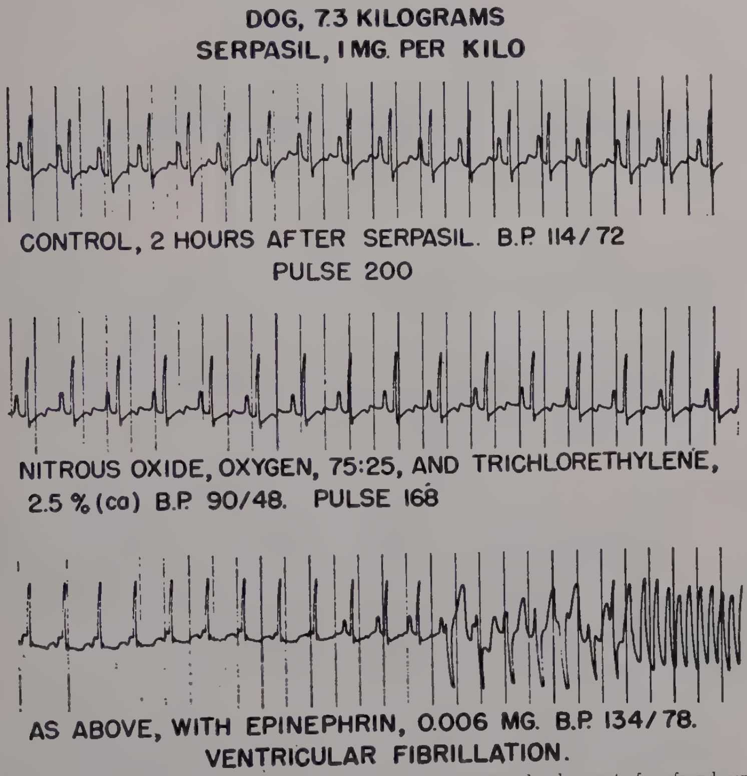

DOG, 7.3 KILOGRAMS
SERPASIL, 1 MG. PER KILO
CONTROL, 2 HOURS AFTER SERPASIL. B.P. 114/72
PULSE 200
NITROUS OXIDE, OXYGEN, 75:25, AND TRICHLORETHYLENE,
2.5 % (ca) B.P. 90/48. PULSE 168
AS ABOVE, WITH EPINEPHRIN, 0.006 MG. B.P. 134/78.
VENTRICULAR FIBRILLATION.

CHART 10. To illustrate, in the dog, that reserpine does not prevent development of profound ventricular arrhythmias.

To illustrate this difference in action of the two compounds in still another manner, experiments were designed to see if chlorpromazine or reserpine would protect against the myocardial irritability which is seen in the presence of trichloroethylene-epinephrine combinations. CHART 9 demonstrates the ventricular tachycardia and ventricular fibrillation which do occur in the majority of animals under these circumstances. In CHART 10, it is noted that reserpine, 1 mg. per kilogram, does not protect the animal against the onset of these fatal arrhythmias. On the other hand, CHART 11 shows that chlorpromazine will protect the heart against the irritant effects of epinephrine.[11]

From these experiments, it may be assumed that chlorpromazine possesses an adrenolyticlike activity which is not shown by reserpine. This activity may have advantages and disadvantages in clinical practice.

Observations During Postoperative Period

Since the action of reserpine is believed to extend at least over a 24-hour period and, since chlorpromazine exerts its effect for six to eight hours, it was believed that dosages of these drugs, administered preoperatively, might have a beneficial sedative action extending into the period following surgery. If the

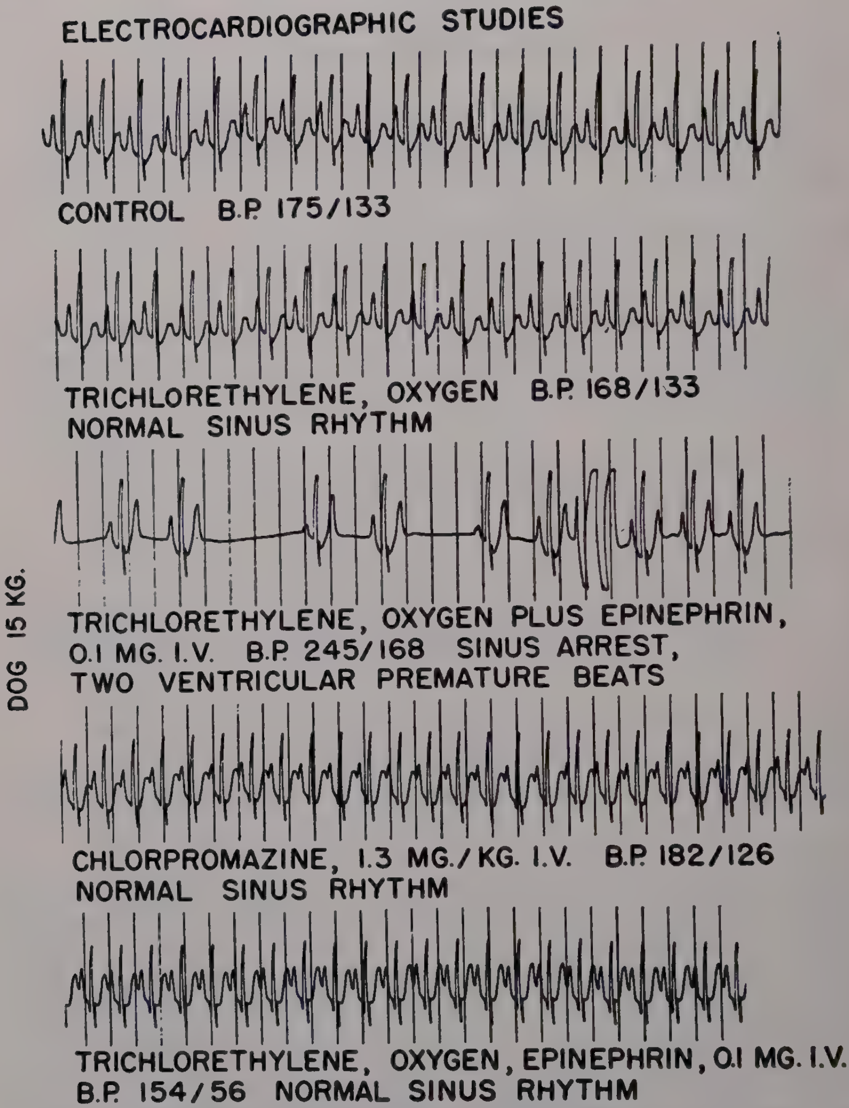

ELECTROCARDIOGRAPHIC STUDIES
CONTROL B.P 175/133
TRICHLORETHYLENE, OXYGEN B.P 168/133
NORMAL SINUS RHYTHM
TRICHLORETHYLENE, OXYGEN PLUS EPINEPHRIN, 0.1 MG. I.V. B.P 245/168 SINUS ARREST, TWO VENTRICULAR PREMATURE BEATS
CHLORPROMAZINE, 1.3 MG./KG. I.V. B.P 182/126
NORMAL SINUS RHYTHM
TRICHLORETHYLENE, OXYGEN, EPINEPHRIN, 0.1 MG. I.V.
B.P 154/56 NORMAL SINUS RHYTHM
DOG 15 KG.

CHART 11. To show, in the dog, that chlorpromazine may prevent arrhythmias associated with trichlorethylene-epinephrine combinations.

cerebral sedative effect of these drugs were sufficient, the amount of narcotic drugs required in the postoperative period might be reduced.

With this end in view, a series of 93 patients was followed carefully for 16 hours following major operative procedures. One third of these patients served as controls, one third received reserpine, 5 mg. intravenously in the preoperative period, while the remainder were given chlorpromazine, 50 mg. intramuscularly before anesthesia (TABLE 4). The internes and nurses who

TABLE 4

TO SHOW TYPES OF OPERATIONS PERFORMED IN PATIENTS OBSERVED FOR ANALGESIC REQUIREMENTS IN POSTOPERATIVE PERIOD

	Chlorpromazine	Reserpine	Control
Cholecystectomy	2	0	2
Gastric resection	5	1	1
Hysterectomy	9	7	8
Laparotomies, misc.	2	1	4
Head and neck, major	4	4	2
Intrathoracic	1	2	7
Extremities, major	5	11	4
Miscellaneous, major	3	5	3

TABLE 5

POSTOPERATIVE NARCOTIC REQUIREMENTS FOLLOWING MAJOR SURGICAL PROCEDURES

	None	0–4 hrs.	4–8 hrs.	8–12 hrs.	12–16 hrs.
Chlorpromazine, 31 patients	6 (19%)	11 (35%)	11 (35%)	16 (51%)	21 (67%)
Reserpine, 31 patients	6 (19%)	8 (25%)	10 (32%)	17 (54%)	11 (35%)
Control, 31 patients	3 (9%)	12 (38%)	19 (61%)	17 (54%)	20 (64%)

To show number and percentage of patients requiring narcotics during various time intervals following surgery.

prescribed and administered postoperative analgesic drugs were not aware of the previous medication, nor were the patients told what they had received preoperatively.

The postoperative analgesic drugs which were given to the patients consisted of morphine, 5 to 10 mg., or meperidine, 25 to 100 mg. TABLE 5 shows the requirements of the 31 patients in each group for the first 16 hours after conclusion of the operation. The first column—"None"—represents those patients who required no analgesics during this period. The remaining columns represent the number of patients who were given narcotics during the time intervals specified.

The relatively small number of cases in this series and the numerous variable factors which play a part in each patient preclude drawing any conclusions regarding the merits of either chlorpromazine or reserpine in the postoperative period. It is of interest that more patients in the experimental series required no postoperative medication at all. For the first eight hours postoperatively, patients who had received chlorpromazine or reserpine appeared to require less medication than did the control group. It is not felt that these figures have any statistical significance, although the possibility of a trend is present.

One other factor pertinent to the postoperative period is worthy of comment. Of the 87 patients who received reserpine in various doses, six, all of whom received 5 mg. intravenously, showed severe nausea and vomiting for as long as 48 hours postoperatively. One of these patients had received three general anesthetics similar to the one associated with reserpine in the previous six months, but none of them was complicated by emesis.

Summary and Conclusions

An attempt has been made to evaluate the use of reserpine as an adjunct to anesthesia and the treatment of the surgical patient. This drug has been compared with chlorpromazine because the two compounds appeared superficially to have some actions in common.

Reserpine showed no marked preoperative sedative action, whereas chlorpromazine reduced fear and apprehension and produced, in many patients, a state resembling sleep. The paucity of action with reserpine may have been due to the recognized latent period between administration and onset of effect.

Injection of reserpine prior to anesthesia did not seem to reduce the total quantities of anesthetic drugs required for surgery. On the other hand, according to clinical estimation, chlorpromazine reinforced the action of hypnotic and analgesic drugs, so that total requirements were less for given procedures.

Reserpine showed little tendency to alter blood pressure or pulse rate in the normotensive patient. In hypertensive patients, the usual finding was a gradual and not significant reduction in blood pressure during the course of anesthesia. In only exceptional instances did the degree of hypotension give cause for worry, and these patients responded promptly and, as expected, to the injection of vasopressor drugs. Approximately 12 per cent of patients who received chlorpromazine showed a reduction in systolic pressure of 40 mm. Hg or more. These patients responded poorly to the less potent sympathomimetic amines such as ephedrine, desoxephedrine, and methoxamine, and in a manner less than anticipated to the more potent drugs Neosynephrine and levoarteronal.

The difference in response to the injection of sympathomimetic amines was substantiated in animals pretreated with reserpine and chlorpromazine. It was noted also that chlorpromazine tended to prevent the severe cardiac arrhythmias associated with trichloroethylene-epinephrine combinations, whereas reserpine had no such protective action. The assumption is made that the phenothiazine derivative possesses some adrenolytic action while the *Rauwolfia* derivative does not.

In the postoperative period, there was no clear-cut evidence, on the basis of data presented, to indicate that either reserpine or chlorpromazine reduced the total amount of narcotic drugs required by patients. Perhaps there was a trend in this direction. It was noted that severe nausea and vomiting occurred in six patients for periods up to 48 hours after receiving reserpine, 5 mg. intravenously.

It is our belief that the administration of reserpine preoperatively in doses of 0.5, 1.0, 2.0, or 5.0 mg., intramuscularly or intravenously, does not contribute substantially to the management of anesthesia or the postoperative care of the patient.

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RESERPINE A NEW ADJUNCT IN THE MANAGEMENT OF RESISTANT HEADACHE PATTERNS: A PRELIMINARY REPORT*

By Bernard M. Barrett and French K. Hansel†
Pensacola, Fla.

Headache is one of the most common of all human ailments. Like all pain, it is a warning that some functional or organic process is playing a part in its production. The over-all incidence of headache in the general population is recorded at about 8 per cent. It is believed, however, that only about 18 per cent of this group find their headaches sufficiently disturbing to seek medical aid. The use of sedatives, analgesics, and antipyretics is still prescribed by many physicians for acute and chronic recurrent types of headache and, when these do not suffice, many of the sufferers are then labeled as psychoneurotic. The incidence of headache is greater in females than males. Professional men, students, and executives appear to be more susceptible to head pain than other groups. Common causative agents enumerated by these individuals are fatigue, eye strain, and, in women, menstruation. The specialists most commonly consulted for relief are the otolaryngologists and the ophthalmologists. Recent investigations in headache problems have resulted in a more logical classification and have thereby given a sounder therapeutic approach to the drugs that may be used in headache treatment. The over-all incidence of poor therapeutic results with present medication is approximately 15 per cent. These poor therapeutic results can be attributed to (1) inability of the patient to tolerate the medication employed; (2) contraindications to the medications that would be feasible; and (3) inability to obtain correction of additional factors which may be psychogenic or endocrine in nature. The classification of headaches into vascular and nonvascular types gives a satisfactory working basis for treatment.

The nonvascular group consists of a rather variable arrangement of many causes. Vascular phenomena may play a secondary part in many of these types. The vascular types have been classified by Hansel as follows:

(1) Allergic headache
(2) Migrainous types
    (a) Classical migraine
    (b) Migraine variants
        (i) Ophthalmic
        (ii) Ophthalmoplegic
        (iii) Status migrainus
        (iv) Abdominal
        (v) Histaminic cephalgia (Horton)
    (c) Tension headache
(3) Temporal arteritis (rare)
(4) Hypertension

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* The reserpine (Serpasil) used in these experiments was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

† Hansel Foundation and Washington University School of Medicine, St. Louis, Mo.

Nonvascular types (which may be secondary vascular factors) are classified as follows:

- (1) Intracranial disease
  - (a) Meningeal irritation (meningitis, hemorrhage, syphilis)
  - (b) Lesions producing pressure (brain tumor, abscess, hematoma)
- (2) Sinusitis—allergy and infection
- (3) Otitic manifestations
- (4) Ocular disturbances
- (5) Neuralgias (trigeminal, occipital)
- (6) Pyrexia, toxic, uremic
- (7) Psychogenic
- (8) Endocrine
- (9) Posttraumatic
- (10) Cervical myositis
- (11) Hypoglycemic

In the routine office practice of otolaryngology, 21 patients were selected from approximately 150 recent cases that had been under observation and treatment for headaches. They consisted of patients who had been subjected to many different types of medication and, in most instances, had seen many physicians without securing any relief from their headaches. By the time they were placed on their present course of therapy, they were in many instances despondent. One professed suicidal intent, and many were extremely apprehensive and emotionally labile to a high degree. These 21 cases may be classified as follows:

- Vascular
  - Allergic headache (1)
  - Classical migraine (1)
  - Migraine variant
    - (a) Ophthalmic (1)
    - (b) Histamine cephalgia (5)
    - (c) Atypical histamine cephalgia (6)
    - (d) Tension (5)
    - (e) Temporal arteritis (1)
- Nonvascular
  - Endocrine (1)

Allergic Headaches

The diagnosis of allergic headache is established on essentially the same basis as other allergic conditions. Usually, a positive family history of allergy is encountered in about 70 per cent of patients, and the past history may reveal manifestations of allergy, such as eczema, urticaria, gastrointestinal or respiratory allergy, including hay fever, before onset of the headache. Allergic headaches are not likely to occur as a single manifestation. There may be prodromal symptoms, such as a gastrointestinal upset, vomiting, distention, polydipsia, edema of the feet and hands, swelling of the face, marked gain in weight or, possibly, urticaria within the first 12 to 24 hours before the onset.

Visual prodromata are not common. The headache is usually generalized, with a sense of pressure, dizziness, and mental confusion—cerebral edema. The headache is of the severe pressure throbbing type not relieved by vasoconstrictors, such as epinephrine or ergotamine, because of the occurrence of cerebral edema rather than vascular dilatation. The terminal phase of the attack is characterized by polyuria, a loss of weight (edema) and, finally, there is a return to normal.

The following case illustrates this type:

N. B.—White, female, married, 44 years of age. Chief complaint: nasal obstruction, heaviness of the head, and soreness above and behind the eyes, intermittent in nature, of approximately six weeks' duration, which have not responded to medication consisting of antihistaminics and nose drops. The patient was skin tested and found to be sensitive to ragweed and atmospheric molds. She was started on allergic desensitization in conjunction with antihistaminics and sedatives to be used at bedtime. On August 9, 1954, there was slight improvement, but the patient still complained of heaviness and pain about the eyes. She was started on multivitamins and bellergal at this time. From August 13 to August 20 there was very little improvement. She was very irritable, very puffy about the face, and highly labile emotionally. On August 28, the patient was started on 0.25 mgm. of reserpine q. i. d., in conjunction with the described therapy. On September 4, she was more comfortable but complained primarily of nasal blockage occurring at night. On September 11, there was continued improvement. The patient was given a bottle of allergenic extract and advised to take the injections at home.

Comment. Inasmuch as reserpine frequently causes some degree of nasal stuffiness, it is felt that its usage should not be routinely employed in allergic headaches until some form or allergic control has been instituted.

Migraine

Classical migraine presents the following diagnostic features:

(1) Family history of "sick headaches"
(2) Typical three-phase attack:
    (a) Visual phenomena—prodromal stage 30 minutes
    (b) Unilateral throbbing headache lasting hours or days
    (c) A period of dull steady ache with nausea and vomiting
(3) Begins early in life—may abate at menopause
(4) May be succeeded by histaminic cephalgia type
(5) Possible relationship to allergy, meniere's disease, epilepsy
(6) Relation to menstruation, puberty, menopause
(7) Psychosomatic factors—tension, indecision, *etc.*
(8) Relief with ergotamine tartrate and caffeine, especially if given early
(9) Appears periodically—attacks often weeks apart
(10) Onset of attack can usually be predicted, therefore medication may be taken early

The following case represents the classical migraine:

B. V.—White, female, married, 69 years of age. This patient had been under office treatment since 1934. At the onset, her chief complaints were headaches, primarily in the morning on awakening, and also in the middle of the night, as well as an inability to breathe well through her nose. A septal deviation was present and this affliction was corrected surgically. The patient had other surgery performed in October and, on November 15, experienced headaches burning in character in the vertex and temporal areas. At this time, it was noted that her blood pressure was slightly elevated, and a medical consultation was therefore arranged. One year later, she complained of occasional headache and vertigo on stooping. At this time, she was placed on nicotinic acid injections and oral medications, which gave relief, but the symptoms continued intermittently. In 1941, she was given a full course of histamine injections and, since nasal cytology indicated an existing allergy, she was placed on antiallergic management as well. During the ensuing years, many episodes of headache, as well as several attacks of migraine, occurred which required hospitalization with intravenous glucose and narcotics. From January through April 1954, the patient was seen practically every week complaining of pain above the eyes, heaviness of the head, and fullness in the nose. Local medication to the nose, antihistaminics, and injections of dust and mold extract were given during this period of time, with improvement. The patient, seen again in October 1954, was complaining of this same difficulty. The same program was instituted. Three days later, she had a severe attack of migraine preceded by scotoma, associated with nausea and vomiting, which required hospitalization. Early in November 1954, the patient had an acute migraine seizure. After that she was given 1 mgm. of reserpine (Serpasil) three times a day (t. i. d.), after meals (p. c.). The patient was last contacted on January 13, 1955, and had been completely comfortable except for a slight nasal stuffiness. She was advised to reduce the medication to one half the dosage.

Migraine Variants

The classification of these headaches is based upon the site, the character of the pain, the frequency and duration of the attacks, and upon the nature of the associated manifestations.

Patients may occasionally present all the cardinal features of classical migraine, except the typical three-phase migraine attack itself. The chief complaints usually follow one of the patterns of the migraine variants. These variants may be grouped as follows:

(1) *Variant in the prodromal phase.* Visual and other nonpainful phenomena are caused by initial vasoconstriction of the cerebral arteries. Headache may never develop or may be mild. The visual and other sensory disturbances may become so pronounced, however, that they form the major complaints.

(a) *Ophthalmic migraine:* The attack usually starts with a central dot before the eyes, followed by scintillating and colored zigzag lines, until there is a considerable gap in the field, often assuming the form of homonymous hemianopsia. There may be a mild accompanying headache, general malaise, vertigo, and sometimes nausea and vomiting. Attacks vary in frequency and may last about 15 minutes, with no residual visual disturbances.

The following case illustrates this type:

E. F.—White, female, married, 35 years of age. Chief complaints: pains about the left frontal and cheek regions and the left ear, associated with photophobia and lacrimation of five months' duration, occurring intermittently one to three times a week. The present attacks were preceded by episodes of blurring of vision in the left eye and a slight tenderness over the left temporal region. She would see spots before her eyes, as well as blurring, and felt as though she were going blind in the left eye. She was treated by an ophthalmologist with vitamin B_{12} and antispasmodics, and the visual disturbances cleared up after two weeks, but now she has headaches. The past history was essentially negative except for a hysterectomy in 1949. The blood pressure was 114/90. The patient had previously taken bellergal, cafergot, histamine, pyribenzamine, and vitamin B_{12} for three weeks. She was started on a dosage of reserpine of 0.25 mgm. four times a day (q. i. d.). Within a few days, there was great improvement, which continued for seven days, but she also had fatigue and weakness. She was advised to reduce the dosage of reserpine to one half. Elixir dexamyl was prescribed for weakness. Three months later, she was still comfortable.

Histaminic Cephalgia (*Horton's Syndrome*)

This migraine variant is a definite clinical entity characterized by well-defined symptoms and signs. It is more common among middle-aged males, and sometimes may succeed a pre-existing typical migraine.

(1) Pain is sudden and severe in onset, of short duration, and subsides abruptly.

(2) The headache is unilateral, but may occur on either side, usually on the one side more than on the other. It involves the orbital, the frontal, the cheek, and the temporal regions, sometimes radiating to the occiput, neck, and shoulder. Lacrimation, rhinorrhea, nasal congestion, and sweating of the affected area usually accompany the attack, but may be absent. On the other hand, these symptoms and signs may be present without the pain. The nasal symptoms may precede the attack.

(3) The typical attack commonly occurs at night or in the early hours of the morning and is relieved, to a great extent, by assuming the erect position or getting out of bed and walking. Several attacks may occur within 24 hours. There is no definite periodicity.

(4) There are no "trigger zones."

(5) No visual prodromata, nausea, or vomiting occur.

(6) There is no family history of this type of headache.

(7) Attacks may be precipitated by the injection of a comparatively small dose of histamine or the ingestion of alcohol.

The following cases are of this type:

W. M. S.—White, female, married, 41 years of age. Chief complaints: burning of the right side of face, starting in the supraorbital region, migrating temporally and into the right mastoid area, of approximately 10 years' duration, occurring one to two times a month, and lasting from several days to a week. It is not associated with nausea or vomiting but with abdominal distention and cramping. The attacks awakened the patient from sound sleep at night. The pains increased in severity, and the attacks had been more frequent during the previous two months. Extensive treatment during a period of 10 years by many physicians had not produced any great relief. Treatment consisted of analgesics, sedatives, histamine injections, intravenous calcium, and general systemic management. The patient stated that if, at the onset, she immersed her head in very hot water she could occasionally abort an attack. During the last severe seizure, intravenous calcium appeared to be beneficial. The past medical history was essentially negative. Surgical history: partial oophorectomy in 1934 and in 1944. She had had two children and had experienced two pregnancies. There was a positive family history of allergy. The patient was started on 1 mg. of reserpine, t. i. d., p. c., in conjunction with intravenous calcium. Four days later she was still having some slight soreness, but felt considerably improved. Four days subsequently, she was asymptomatic and had a sense of well-being and serenity. One month later, improvement maintained.

D. B. T.—White, female, married, 26 years of age. Observed for the first time August 3, 1954. Chief complaint: headaches practically all her life. Positive family history of sick headaches. She recently noted that, when driving a car, her neck would become stiff, and severe pains were localized in the occipital and cervical regions. Usually, she had daily supraorbital headaches which migrated bitemporally. The past history was essentially negative, both medically and surgically. The recent medical examination was within normal limits. The patient had had itching on the arms and shoulders during the past summer which she felt was due to exposure to sun rays and, during the current summer, she had had a slight recurrence of this difficulty. She had also noted that, at times, there was a tendency for her hands to seem to go to sleep. The ear, nose, and throat examination was essentially negative, except for a septal spur on the right side and moderately enlarged tonsils. This patient was started on treatment consisting of histamine injections, bellergal, mephate, and pabalate. On August 6, there was slight improvement. One week later, an acute episode of itching occurred, for which antihistaminics were prescribed. Two weeks later she was free of headache for three or four days, but still had some itching. After receiving intermittent injections of histamine and taking antihistaminics and bellergal, she was relatively comfortable for about six weeks. One month later, she stated that a very severe episode of supraorbital headache occurred the previous day and she was quite despondent. At this time, she was started on therapy with reserpine, consisting of 0.25 mgm. three times a day t. i. d., p. c. After 10 days, there was great improvement and, for six weeks thereafter, she was completely comfortable and was advised to continue on therapy with reserpine.

A. E.—Colored, male, 42 years of age. First seen on June 18, 1952. Chief complaint: shooting pains, starting in the right cheek, radiating to the temporal region, forehead, and above the right eye, occurring at no particular time of day but also at night. These attacks, more or less continuous since 1944, alternated with episodes of dizziness. Treatment was started on injections of histamine and nicotinic acid, and also oral therapy with nicotinic acid. Cafergot was prescribed for acute attacks. The patient improved on this program. Nine days later, he complained of having pain at night. He was therefore started on bellergal for interval therapy. The patient was kept relatively comfortable on this program. Nine months later, he had an acute attack, and additional attacks occurred three and six months afterwards. All of these seizures were controlled by instituting the previous therapy. Nine months subsequently, the patient was experiencing some dizziness and an occasional headache. Previous therapy was reinstituted with some improvement. The patient still had slight difficulty when seen 30 and 60 days later. Then he was started on therapy of reserpine, 0.25 mgm. q. i. d. and, after a month, he was completely comfortable but was experiencing some nasal stuffiness and occasional episodes of weakness. He was advised to reduce the reserpine therapy 0.125 mgm. t. i. d., p. c., and elixir dexamyl as needed for weakness was prescribed. The patient has continued on this therapy and has been completely comfortable.

J. M. D.—White, male, married, 37 years of age. History of headaches two or three times a month all of his life, associated with deep-seated pain in the back of the neck and soreness behind the eyes. The headaches awakened him from sound sleep at night. Bellergal orally and histamine by injection were instituted. After 11 days, there was slight improvement. After three weeks, he was still having intermittent exacerbation. The administration of 0.25 mgm. of reserpine four times a day was therefore begun. Within seven days he felt better, but the medication was causing weakness. He was advised to reduce the dosage to 0.125 mgm. t. i. d. and 0.25 mgm. at bed time. He continued on this program without any acute episodes.

M. W. L.—White, female, widow, 47 years old. First seen September 23, 1953. At that time, her chief complaint was headache, throbbing and burning in character, more or less limited to the left temporal region, but prone to migrate anteriorly to the frontal region and eye and, posteriorly, to the occipital region, occurring intermittently during the past two years and lasting from a few minutes to several days. Patient has also been awakened from sleep by attacks. The general examination performed by her family physician was essentially negative. The ear, nose, and throat examination was essentially within normal range except for a moderate septal deviation to the left side. Initial treatment consisted of injections of histamine, with bellergal and cafergot orally for acute episodes. On September 30, she had experienced some improvement. On October 5, she was given dihydroergotamine (DHE-45), for relief of an acute episode. Fever occurred with this attack. On October 8, there was slight improvement. From October 8 through October 23 she was completely comfortable while receiving injections of histamine. During this period, interval therapy with bellergal was continued. On December 16, she had an acute episode which had not been relieved by cafergot. DHE45, at this time, gave very slight relief. On December 20, another acute attack required injections of DHE45 and codeine for control of the episode. She was relatively comfortable from December 1953 to October 11, 1954, on interval therapy of bellergal. After an acute episode on October 11, 1954, injections of histamine were resumed. She was also given DHE45 and antihistaminics, as well as mephate. On October 25, 1954, there was very slight improvement. Reserpine therapy consisting of 0.25 mgm. t. i. d., p. c., was begun. From October 25 through November 15, 1954, she was completely comfortable. Then reserpine therapy was reduced to 0.1 mgm. t. i. d., p. c. When last seen, on December 25, she indicated that she had been completely comfortable but had contracted a moderate upper respiratory infection and was having an acute episode. She was advised to continue her reserpine therapy and was given local nasal medication as well as antibiotics.

Atypical Histamine Cephalgia

On the whole, the patients with atypical attacks had complaints which were very similar to those of the classical type. The headache was almost always unilateral and had the same distribution. The attacks were of varying duration, some being short and some very prolonged. A majority of the patients had night attacks and, in many instances, the headache came upon arising in the morning. Nausea and vomiting, visual disturbances, and a positive family history were rare, so that their classification as migraine did not seem justified. Alcohol frequently precipitated attacks. In some instances, the headaches in women were more pronounced with the menses or pregnancy. On the whole, the atypical group presented a history of less severe attacks than the typical group. There was also no definite history of sweating, tearing, and nasal stuffiness. Because of the fact that a number of these patients responded to histamine therapy, it appears justifiable to classify them as a mild type of histaminic cephalgia. Although the area most commonly involved in typical cases is confined to the frontal, ocular, and cheek regions, the pain is commonly referred to the temple, mastoid, and occipital regions. Occasionally, the vertex area is involved. This would suggest that any of the cranial vessels may be the site of reaction. A significant number of cases have also been encountered in which pain and discomfort referred to the parotid, pharyngeal, or laryngeal regions could be explained on a vascular basis, as the relief of symptoms was produced by histamine therapy. The most interesting of this group of cases is the so-called globus hystericus type, in which the symptoms are referred to the region of the larynx.

The following cases are of this type:

G. L. W.—White, male, single, 26 years of age. First seen January 17, 1951, with chief complaint of vertigo and tinnitus associated with nausea, vomiting, and supraorbital headache. After 12 days, this attack was completely controlled by nicotinic acid and a salt-free diet. A recurrence of difficulty occurred February 20, 1951, following a hemorrhoidectomy. This difficulty was again controlled by nicotinic acid and a salt-free diet. In March 1951, the patient complained of a headache which was associated with some mild nasopharyngeal infection which responded to treatment with nicotinic acid and antibiotics. In August 1951, he had a recurrence of the vertigo and supraorbital headache, which again responded to the above therapy. In October 1952, he complained of dizziness and supraorbital pain of approximately three weeks' duration. There was some superimposed secondary infection in the paranasal sinuses. This attack was soon controlled by therapy of nicotinic acid and histamine injections. On February 3, 1953, supraorbital headache appeared. This eventually responded to injections of histamine. On September 9, 1953, he complained of vertex headache of two or three days' duration. This attack was controlled by nicotinic acid and bellergal. By September 24, he was completely comfortable. In November 1954, he complained of dizziness and vertigo, burning pain over the vertex, and slight nausea and vomiting. Injections of histamine and nicotinic acid were begun, and he was also given bonamine and potassium chloride orally. The dizziness improved in that it was less evident. He continued to have headache, however, which had migrated to the supraorbital region and was associated with nausea and vomiting. On December 7, 1954, therapy with 0.25 mgm. of reserpine, t. i. d., p. c., was begun. On December 14 he was completely comfortable and was advised to continue the reserpine therapy.

W. F. E.—White, female, married, 44 years of age. This patient had been observed intermittently since July 30, 1951, during which time the chief complaint was tinnitus which was relatively controlled by histamine injections and multivitamins. During an exacerbation of the tinnitus in October 1953, she complained of muscular cramps in both upper extremities, and was started on therapy of mephate capsules as well as injections of multivitamins. In July 1954, she complained of soreness in the cervical region and exacerbation of tinnitus. At this time, she was started on therapy with bellergal, multivitamins, and histamine, and was greatly improved when last seen in August 1954. In December 1954, she complained of a burning sensation over the vertex of the skull and soreness in the left ear, off and on for about one month, which had not been controlled by her previous medication, namely, bellergal and multivitamins. She had been on interval treatment of these medicaments since August. This patient was started on 0.1 mgm. of reserpine, t. i. d. When seen on December 16, she was greatly improved, and she was advised to continue the treatment. In January she was completely comfortable.

S. L.—Colored, female, married, 51 years of age. Was first seen in December 1953, complaining of dizziness associated with tinnitus in left ear and pain, throbbing in character, in the right side of neck, moving down to the right shoulder, of three months' duration. She was slightly hypertensive. Her blood pressure was 170/80 and she was under treatment by an internist for this condition. Six months previously, she had had kidney stones removed. This episode was relieved by potassium chloride and bentyl hydrochloride with phenobarbital. The patient was subsequently seen in July 1954, when she had the same tinnitus and pain in the neck. These difficulties had not responded to previous medication, which she had tried several weeks. At this time, she was accordingly given 1000 μg. vitamin B_{12} intramuscularly and started on a therapy of mephate capsules as well as multivitamins. In August 1954, she indicated that she had never been completely free of her pain. At that time, she was started on therapy with 0.25 mgm. of reserpine, q. i. d. On October 8, there was improvement. She was advised to continue on this therapy. On December 7, she had pain deep in the occipital region and in the vicinity of the mastoid migrating down the right side of neck, and also a headache over the right temporal region, more or less daily in occurrence. The medical examination was essentially negative. She had discontinued her reserpine after using it for two weeks, as she had been relatively comfortable. She was started again on reserpine therapy, 0.25 mgm. q. i. d., and has been comfortable since.

M. G.—Colored, female, married, 64 years of age. First observed in August 1943, complaining of headaches and slight vertigo of approximately one week's duration. The headaches were primarily described as being sensations of heaviness and soreness above and behind the eyes. The eyes were refracted, and she was given a prescription for empirin compound. In October, she was improved, but still had some slight dizziness. In February 1948, she again had a headache which was more or less continuous. At this time, injections of histamine were begun and, by March 12, was relatively comfortable, although she was still having occasional headaches. She was given histamine injections two to three times a week until April, when she was relatively comfortable. In July, she had a recurrence of the headaches, which again responded to histamine treatment. In 1949, she required several courses of histamine treatment. In 1950, there was response to a course of histamine therapy. In 1951, two recurrences responded to histamine therapy. In 1954, histamine therapy in conjunction with donnatal plus and bonamine for headaches and dizziness was given. She was kept on the donnatal plus approximately three months. In September, there was a recurrence of the headache and, in October, she was started on 0.25 mgm. of reserpine, q. i. d. Weakness and numbness of extremities and slight nausea appeared while taking reserpine. She was advised to reduce the dosage to 0.125 mgm. She has continued on this dosage without difficulty and has been relatively controlled, even though she still had occasional fullness about the eyes. The reserpine appeared to have improved her outlook, so that her headaches were not as great a cause of concern as they previously were. During this time, she had been under medical supervision and had received supplemental hormonal treatment in 1953 and 1954 consisting of estrogens and thyroid.

D. B.—White, female, married, 65 years of age. Unilateral left-sided headaches, sudden in onset, awakening patient from sleep at night. These headaches had not responded to intensive general systemic buildup and intermittent courses of histamine and bellergal over a period of two years. Reserpine therapy was started on August 13, 0.25 mgm. q. i. d. On August 25, the patient noted improvement and, in October, she was still on medication and fairly comfortable. She had been seen approximately twice a month and was last seen on January 11. Her major complaint at that time was nasal stuffiness, especially at night. She was completely free of head pain and was advised to reduce the reserpine to 0.125 mgm. t. i. d.

R. B.—White, female, married, 34 years of age. First seen February 18, 1952, complaining of aching in vertex area for several days. There was no prodromal, nausea, or vomiting. The past history was essentially negative except for an appendectomy, a tonsilectomy and adenoidectomy, and dental extractions of all uppers six months previously. The patient was given injections of nicotinic acid supplemented by oral therapy and local medication to the nose. On March 17, she complained of choking and fullness of the throat. This condition was relieved by local treatment to the nose. In April 1952, she complained of fullness above the eyes and some slight sensitivity to light. Ocular examination revealed a moderately refractive error that was corrected. At this time, histamine treatment was begun, and cafergot was prescribed for the acute episodes. There was continued improvement on this program, which was extended through December 5. On January 20, 1953, the patient had a supraorbital headache associated with throbbing in the temporal regions. She was then started on bellergal interval therapy in conjunction with histamine injections. In April 1954, she complained of occipital headache which was aborted by injections of DHE45, and then she was started on therapy with Fiorinal. In August 1954, she complained of pain around the right temporomandibular region, attributed to a slight irritation in the external ear canal, which appeared to be grossly normal. X rays of this area revealed no gross abnormality. Therapy with histamine and nicotinic acid was started. Pain persisted in spite of intensive therapy with histamine, pabalate, mephate, and vitamin B_{12}. The pain was pounding in character. The attacks occurred primarily at night, lasting from five minutes to several hours, but would leave some residual soreness. On October 6, treatment with 0.25 mgm. of reserpine, q. i. d., was instituted. On October 9, there was improvement. Four days later improvement continued, but the patient complained of numbness of the extremities. The dosage was reduced to 0.125 mgm. On December 7, she had an incipient upper respiratory infection (URI) and some slight globus, but she had been completely comfortable previously on her therapy. On December 17, she complained of some throbbing about the right side of the neck in the vicinity of the larynx. Some very slight nasopharyngitis also was present. She had discontinued her reserpine during the previous week, but was advised to resume this therapy with local medication to the nose and throat. One week subsequently she was comfortable.

Tension Headaches

Tension headaches develop in normal individuals who may or may not necessarily complain of migraine headaches. Periods of anxiety and tension cause vessel hypertonicity, which is followed by vascular dilatation and headache.

(1) Headache is dull, nonthrobbing in type, not usually localized in one area.

(2) Familial history, nausea, and vomiting are usually absent.

(3) Attack develops slowly during or after a prolonged period of tension, stress or anxiety.

(4) This type is related to migraine only because of the vascular mechanism common to both.

Tension and muscle tension headache are not the same phenomena. The latter is caused by sustained contractions of the muscles of the head and neck, and is not infrequently associated with all types of headache, especially those of longer duration. It may persist for some time after the subsidence of the attack.

B. R. K.—White, female, married, 43 years of age. Supraorbital headaches, which date back to a URI. She was first observed on April 19, 1954. She had been on therapy with bellergal for this difficulty, as recommended by a previous physician, without any improvement. She was started on mephate, vitamin B_{12}, and local therapy to the nose. From May 19 to the 26, there was some improvement. From June 3 to June 22, she was relatively symptom free. On July 17, she had a recurrence of her headache which was not relieved by the previous medication, and required narcotics for the control of pain. On July 31, as well as on September 16, there was a recurrence of this difficulty. On October 1, the patient was still having headaches, which were improved by injections of DHE45. Reserpine, 0.125 mgm., t. i. d., p. c., and 0.25 mgm. at bed time was prescribed. There was great improvement on continuing this treatment. On January 11, 1955, she was comfortable but still having slight heaviness about the eyes. She had been also on hormonal treatment during the past year.

G. S.—Colored, female, married, 23 years of age. Chief complaint: fullness in the left side of the throat and a sensation of lump in the throat. This patient was very apprehensive, and fearful of having cancer. This was believed to be a case of globus. The basal metabolic rate (BMR) was essentially normal. The patient was started on bellergal and histamine injections on August 12, 1954. By September 14, there was no essential improvement, so reserpine was given. On September 30, there was definite improvement, but the patient complained of numbness and weakness. The dosage was reduced to 0.125 mgm., t. i. d., p. c., and improvement occurred on this therapy.

R. B. M.—White, male, married, 39 years of age. Chief complaint: pain about right eye and right side of head with sudden onset and of fleeting duration. The pain started usually in the occipital region and migrated anteriorly. It was not improved by histamine, bellergal, vitamin B_{12}, mephate, and multivitamins administered from June 26 through September 9, 1954. A large septal spur was embedded in the inferior turbinate on left side. This was corrected surgically, but the patient still complained of the initial difficulty and feared brain tumor. On October 10, 1954, 0.125 mgm. of reserpine, t. i. d., and 0.25 mgm. at bed time was prescribed. There was improvement after four days. During November and December, he had been comfortable.

J. D.—White, female, married, 20 years of age. First seen July 20, 1954. This patient complained of pain in and about the right ear, migrating down the right cervical region, and she also had globus symptoms. This attack was preceded by a mild URI, and her past history was essentially negative except for a tonsilectomy and adenoidectomy during childhood and an allergic rhinitis. She was given local medication consisting of nose drops, antihistaminics and bellergal, to take internally, and was advised to return for an allergic investigation. In August 1954, she complained of pain in the right temporal region of approximately two months' duration, migrating down the right side of the neck. She indicated that she had some slight improvement from the previous medication and had continued on it, but that it was of no help to her during her present attack. The pain was throbbing in character and migrated from the ear down to the base of the tongue. It did not appear to be associated with any URI and there was no particular time of day that it was prone to occur. The allergic investigation at this time revealed extreme sensitivity to ragweed and grass pollens, as well as to dust and atmospheric molds. She was started on a program of desensitization, antihistaminics, bellergal, and injections of massive doses of vitamin B_{12} consisting of 1000 μg., three times a week for two weeks. The BMR, chest films, and barium swallow were essentially normal. Slight improvement occurred during the period from October 14 to November 15. The pain, however, still persisted and could not be controlled by allergic measures alone. This patient was extremely apprehensive, and felt as though there was some possibility of cancer. The patient was started on therapy of 0.1 mgm. of reserpine, t. i. d., before meals. On November 27, there was considerable improvement and, when last seen on December 15, the pain had completely subsided.

W. B. R.—White, female, married, 57 years of age. This patient has been under observation since July 21, 1951. Although the primary difficulty was an allergic rhinitis associated with supraorbital headaches and pain in the cervical regions, she always had an abundance of varied complaints and exhibited a great deal of tension and apprehension. She had been on medical treatment for gall bladder trouble and was taking belladenal for this condition. During the remainder of 1951, this patient's condition was greatly improved by allergic desensitization, antihistaminics, and supplemental vitamin therapy. She required approximately 10 booster doses during 1952. In February 1953, she complained of headaches. She was therefore started on additional desensitization and allergic control in conjunction with Fiorinal. On June 29, 1953, she was relatively asymptomatic. On August 4, she complained of soreness above the eyes and supraorbital pain of a throbbing character, radiating to the vertex of the skull. This pain had been more or less continuous during the previous few months. She had resumed previous medication without any improvement. She was started on 0.25 mgm. of reserpine, t. i. d., p. c., and, on August 10, she was relatively free of pain. When last seen, on August 26, she was symptom-free and was advised to continue on her medication for several months, and then report if she had any additional difficulty.

Temporal Arteritis

Temporal arteritis is characterized by periodic attacks of constant throbbing pain, chiefly in the temporal region. The arteries in the temporal fossa become distinctly palpable during the headache period. Most patients have fever from the onset, sometimes persisting for months. Often associated with this fever are malaise, weakness, and profuse sweats. The lesion is thought by some to be related to chronic periarteritis and a manifestation of a widespread arteritis.

The following case is of this type:

B. J.—White, female, married, 43 years of age. Chief complaint: pain behind left eye and over entire left side of head, radiating to the occipital region and about left eye, more or less daily in occurrence. The patient had been seen by four previous physicians without much benefit. She was hypertensive, supposedly controlled by current medication. Her blood pressure on her initial visit, May 24, 1954, was 150/100. The pain appeared primarily localized along the distribution of the left temporal artery. This patient was given injections of vitamin B_{12}, tablets of hydergine, and sedation without any benefit. Even though, during this time, her blood pressure did not exceed 150/100, she complained daily and was exceedingly desperate. On July 23, a local injection to the left temporal artery was performed with Novocaine. The patient experienced some slight relief. On July 25, this treatment was repeated, and then the patient was started on reserpine, q. i. d. She returned on August 2, and reported that she was asymptomatic for the entire week. On August 11 and on August 26, she was still comfortable. On October 8, there was an exacerbation of symptoms, so the left temporal artery was injected. In December, she had been completely comfortable on treatment with no acute episodes. The artery was injected and treatment continued. She was gratified with the results of treatment.

Endocrine Headaches

There are many instances in which the endocrines must play an important part either as primary or secondary factors in headache patterns. The influence of puberty, menstruation, pregnancy, and menopause on the clinical course of headache is well known, and these factors must be duly considered in the management of the patient. The thyroid may also play a definite part.

The following case is this type:

J. W. B.—White, female, married, 38 years of age. Tinnitus was aggravated at the time of the menstrual cycle and was associated with tightness in the right side of neck and with throbbing pain over the right side of the head. Attacks occurred one to two times a month, and had lasted from several hours to several days for three years. These attacks were not associated with nausea and vomiting, but usually required bed rest for relief. There was a positive family history of sick headaches and a positive family history of allergy. The patient was first seen on May 11, 1954. Blood pressure was 118/80. MRB and medical examination were within normal range. Therapy consisted of histamine, B_{12} 1000 μg. and antispasmodics, along with donnatal plus. On May 15, there was slight improvement. B_{12} and histamine injections were repeated. On May 20, the injections were repeated. On May 25, the patient indicated that the condition was aggravated, and a severe cramping in the neck occurred after the previous injection. Bellergal and mephate were prescribed. On June 1, there was improvement and, on June 9, the patient's condition was more satisfactory. On July 1, the patient was comfortable. She was advised to continue treatment. On August 2, the patient was having a very severe exacerbation, even though she had continued on bellergal and mephate since the previous visit. All medication was discontinued, and 0.25 mgm. of reserpine, q. i. d., was substituted. The next day, weakness and numbness in the extremities and abdominal distention appeared. She was advised to take 0.125 mgm. of reserpine instead of 0.25 mgm. On August 27, she stated she was unable to tolerate even 0.125 mgm. of reserpine, and that her present attack was soon followed by menstruation. Mephate was again given as well as dexamyl, to improve the over-all mood. A gynecological consultation suggested that androgens should be administered one week before the next menstrual cycle. On October 6, the patient was having a severe headache and, at this time, in view of the positive family history, she was started on antihistaminics, and an attempt to start 0.1 mgm. of reserpine, t. i. d., was made. On December 17, she stated she was not able to tolerate reserpine, and she was having an acute flareup of her head pain. This was at the time of the menstrual cycle. DHE45 at this time gave slight relief. She was advised to continue on antihistaminics. On December 22, she was relatively comfortable. This pain appeared to be primarily a nonvascular endocrine headache with underlying allergy and tension, and was not benefited by medication.

Discussion

The side effects which have been encountered with reserpine have consisted of nasal obstruction, muscular aches and pains, numbness of the extremities, and weakness. These effects could be eliminated by a reduction of the dosage employed and also by supplemental treatment with nose drops and dexedrine. Two patients refused to try a reduced dosage of the drug because of the peculiar sensation they had initially experienced. It is now our routine to start patients on 0.1 mgm. t. i. d., p. c., and then increase or decrease the dosage as indicated. Some therapeutic results will usually be evident after one week and, within two weeks, definite response is usually evident. After about three weeks, dosage may be reduced for maintenance therapy.

The above series represents a group of patients who were resistant to varied forms of treatment which included cafergot, DHE45, bellergal, endocrine treatment (thyroid and estrogens and androgens where indicated), and general systemic treatment as well as muscular relaxants and antispasmodics such as mephate, donnatal plus, and local anesthesia to affected areas. The cases have been classified as above but, obviously, there are many concomitant complicating factors. All had varying degrees of tension which obviously, in many instances, would become dominant after a long period of therapeutic failure. The majority of these have been improved so that they are now more responsive to their indicated treatment and, in many, no additional therapy is necessary except a maintenance of this program. In additional patients now under observation, the dosage employed is far less than initially used in this group, and the results appear to be favorable.

Pharmacologic studies on the circulatory effects of reserpine show that it gradually lowers the blood pressure in anesthetized cats, rabbits, and dogs. As with the sedative effect, the decrease in blood pressure occurs slowly, and the maximum degree of hypotension is attained only after some time. It appears to be characteristic of reserpine that the hypotensive effect can not be increased beyond a certain point despite a considerable increase in dosage. The antihypertensive effect apparently is caused by a protective influence upon the central autonomic centers against stimuli of various types coming from peripheral or even cortical areas. According to Plummer and his associates, all observed effects such as sedation, reduced emotional response, peripheral autonomic alterations, and circulatory changes are explicable on the basis of partial suppression of sympathetic predominance at the hypothalamic level.

Although this group of cases of vascular headaches is comparatively small, preliminary observations suggest that reserpine in smaller doses is effective in controlling symptoms and, in some instances, may be effective in breaking the cycle of attacks.

A great advance in the therapeutic management of these functional headaches came with the introduction of the use of histamine, reported by Horton about 15 years ago. Later, nicotinic acid was also found to be of value, either when given alone or as a supplement to histamine therapy. Horton's method of administration of histamine consists in the daily intravenous injection of one half to one milligram daily, or by subcutaneous injections of a 1 to 10,000 solution, beginning with 0.25 cc. twice daily and gradually increasing to a maximum of 1 cc. daily, and then, later, extended to one week or longer intervals. By this method of therapy, a maximum tolerance to histamine is maintained.

It is noteworthy that, when histamine is injected slowly by the intravenous method, no precipitation of an attack of headache is likely to occur; but if 0.10 cc. of a 1 to 1000 solution, or 0.10 mgm. is injected subcutaneously, an attack may be induced. Our results, extending over a period of 15 years in a large series of cases, have been most satisfactory when employing smaller or optimum doses of from 0.10 cc. of a 1 to 1,000,000 to 0.10 cc. of a 1 to 100,000,000 dilution at intervals of three to four days to a week, until the cycle of attacks is broken. In employing this method, we have noted that doses larger than the optimum may cause an attack, and that smaller doses may have no therapeutic effect.

In the treatment of hypertension with the hydrogenated alkaloids of ergot, Grenfell noted that optimum dosages, given at certain intervals, produced the most satisfactory results. He observed that if one cc. (or 0.3 mgm.), which was the standard dosage, was injected daily for one week, there was no fall in the blood pressure but that, when given every two to three days, a fall was gradually produced. Subsequent intervals could be extended to once every two weeks with a maintenance of the therapeutic effect.

These observations suggest that large doses may produce a tolerance response, either with no therapeutic effect or with an aggravation of symptoms. Therefore dosage, as well as intervals of administration, may be important in obtaining the most satisfactory therapeutic response.

In the treatment of this series of cases of vascular headaches, an average optimum oral dosage of 0.10 mgm. of reserpine, two to three times daily, appeared to give the most satisfactory results. Further observation may show that these intervals can be gradually extended with a maintenance of therapeutic effect.

In the management of vascular headaches, the so-called vasodilator type described by Horton has been the most responsive to histamine therapy and to the administration of drugs, especially the ergot compounds for symptomatic relief. The tension and migraine types of headache have presented more different problems as the results with all known types of therapy have not been very satisfactory. Preliminary observations indicate that reserpine may prove to be an important adjunct in the management of these types.

Summary

Preliminary observations on the management of functional vascular headaches indicate that reserpine in optimum doses is of definite value as a therapeutic adjunct, especially in the treatment of the resistant patterns as represented by the tension and migraine types. It is also effective in the so-called histaminic cephalgia type, which represents the majority of all types of vascular headaches. Reserpine, therefore, appears to be effective in all vascular headaches, regardless of the basic mechanisms involved in the various types under consideration.

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THE USE OF RESERPINE AS AN ADJUNCT IN THE MANAGEMENT OF PATIENTS WITH CHRONIC BRONCHIAL ASTHMA AND CHRONIC PULMONARY EMPHYSEMA: PRELIMINARY STUDIES

By Maurice S. Segal and Ernst O. Attinger
Department of Medicine, Tufts College Medical School: and the Lung Station (Tufts), Department of Inhalational Therapy, Boston City Hospital, Boston, Mass.

Anxiety, fear, insecurity, restlessness, nervousness, insomnia, mood and personality deviations, and hypertension are commonly encountered in the management of the patient with chronic bronchial asthma and chronic pulmonary emphysema. Accentuation of these symptoms and a frank "alert state" may be contributed to by the very medications which these patients require, namely: aminophyllin, adrenergic compounds, and the corticosteroids. The present study was undertaken to determine what role in the echelon of therapy reserpine might play in view of its tranquilizing influence in patients with hypertension and nervous disorders. The study was divided into two parts: (1) Clinical Observations and (2) Laboratory Studies.

1. *Clinical Observations*

These studies consisted in evaluating the effects of oral reserpine (Serpasil) in doses of 0.1 to 0.25 mg., administered three times daily over periods of two weeks to six months in 56 patients. These patients generally required aminophyllin and bronchodilator aerosols for symptomatic control. Thirty-two patients received, in addition, corticosteroid therapy, and six received intravenous (i.v.) ACTH (during status state).

Good effects observed consisted of the following: 4 patients noted lessening of dyspnea; 22 noted a sense of greater security and relaxation—seemed less jittery and disturbed and, on the whole, better able to tolerate their stresses; and 8 noted no change in their status. The best effects were observed in patients with manifestations of aminophyllin or epinephrine alertness—jitteriness or insomnia; in those troubled by anxieties and "pepped up" feelings due to corticosteroid therapy; and in those with associated hypertension. *Side effects* were observed in 22 patients consisting of fatigue or sleepiness in 6 patients, stuffy nose in 6, fullness or tightness in the chest in 6, anorexia in 2, and nausea in 2.

2. *Laboratory Studies*

The effects on cardiopulmonary function of the administration of 1 mg. of reserpine intravenously were carefully studied in one patient with chronic bronchial asthma and two patients with chronic pulmonary emphysema. Employing the 4-channel Sanborn recording unit, simultaneous records of pneumotachographic tracings (air-flow rates), intraesophageal pressures, intravenous pressures, and intra-arterial pressures were recorded. When indicated, direct air-flow volumes were recorded on one channel by electrical integration of the air-flow rates. Arterial blood gas studies were obtained when indicated, and computations of cardiac output, dead space, minute ventilation, alveolar-arterial oxygen gradient, lung compliance, and the mechanical resistance to air flow were obtained from the above data.

The first patient studied was a 21-year-old man with chronic bronchial asthma (FIGURES 1 to 5). We have consistently demonstrated that intravenous Mecholyl induces bronchoconstriction in subjects with chronic bronchial

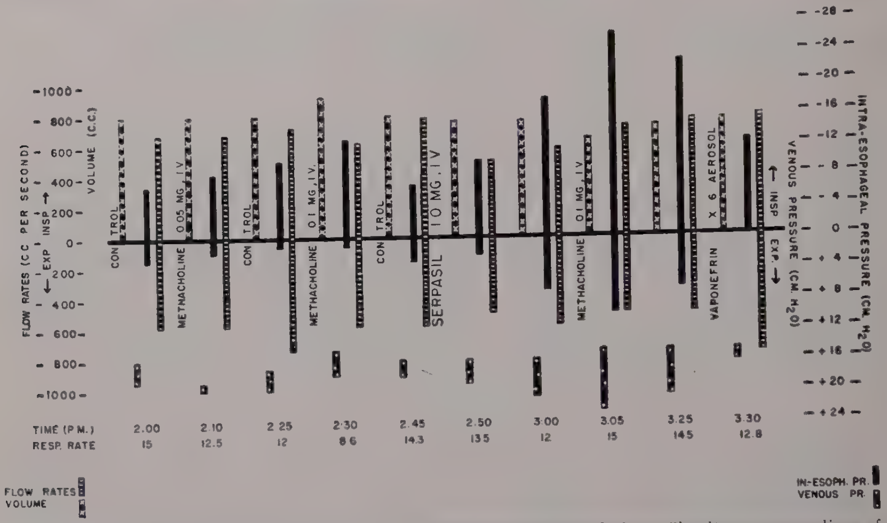

FIGURE 1. The effect of reserpine 1.0 mg. i.v. on induced bronchoconstriction. Simultaneous recordings of venous pressure, intraesophageal pressure, pneumotachogram (air flow rates), and tidal volume.

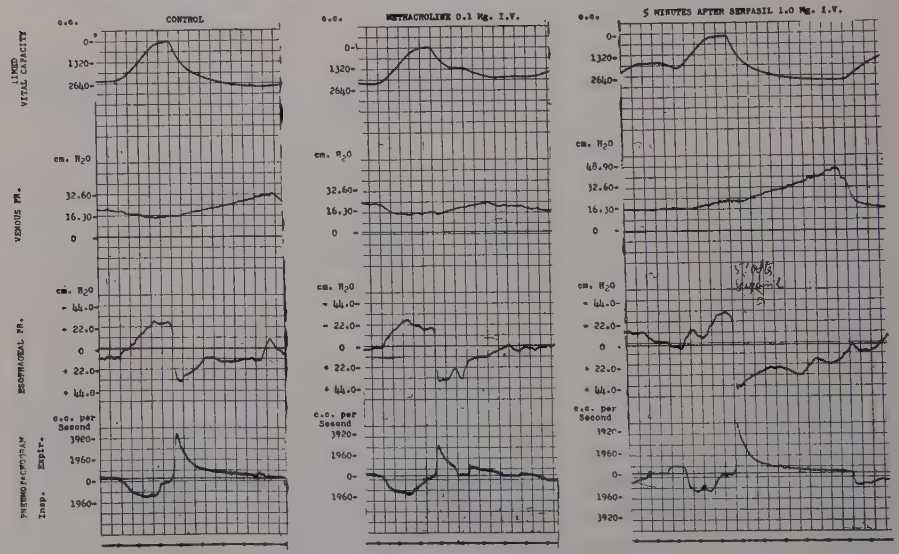

FIGURE 2. Simultaneous recordings of timed vital capacity, venous pressure, intraesophageal pressure, and pneumotachograph at rest (left), after methacholine 0.1 mg. i.v. (center) and after reserpine 1.0 mg. i.v. (right). Note: Glottis closure in center tracing; ball valve mechanism in reserpine tracing.

asthma. Certain protecting drugs; *e.g.*, aminophyllin and adrenergic preparations, when given first, effectively protect against the subsequent effects of Mecholyl. This is referred to as the protection study technique.[1]

In FIGURE 1, it will be noted that after i.v. Mecholyl there was a slight drop in venous pressure, increase in the intraesophageal pressure difference, and a decrease in both the inspiratory and expiratory flow rates. After these effects wore off and the control state returned, 1 mg. of reserpine was administered intravenously. After five minutes, there appeared an increase in the intraesophageal and intravenous pressure difference and a decrease in the inspiratory and expiratory flow rates. These effects were even more marked at the end of 20 minutes. Then i.v. Mecholyl was again administered. There appeared a tremendous increase in the intraesophageal pressure difference, an increase in venous pressure, and a decrease in the inspiratory and expiratory air-flow rates. After 20 minutes, as the Mecholyl effects wore off, these changes were less marked but nevertheless still worse than noted in the control state. Finally, Vaponefrin (bronchodilator) aerosols were given with a striking improvement as all of the values returned to the control state.

A similar acute study was carried out in this patient, substituting Timed Vital Capacity (T.V.C.) relationships in place of the Tidal Volumes (FIGURES 2, 3, and 4). These relationships are most accurately recorded, resistance free, on the pneumotachographic tracing. This procedure must be carried out properly for, when executed too rapidly, expiratory ball-valving may be seen immediately on the recording.[2,3] Following Mecholyl i.v., there appeared a decrease in the T.V.C. and a decrease in the air-flow rates. Twenty minutes after 1 mg. reserpine i.v. there was noted a marked reduction of T.V.C., an increase of the intraesophageal pressure difference and a decrease in the air-flow rates

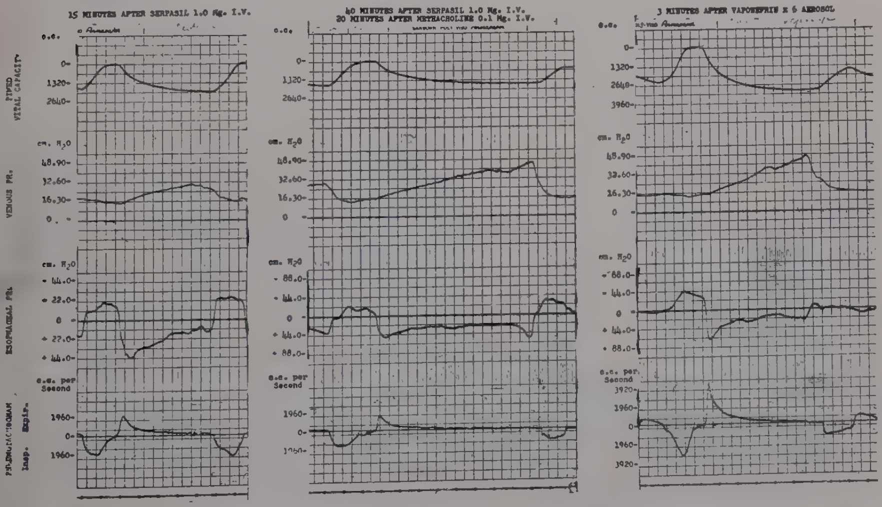

FIGURE 3. Simultaneous recordings of timed vital capacity, venous pressure, intraesophageal pressure, and pneumotachograph 15 minutes after reserpine (left), 40 minutes after reserpine and 20 minutes after methacholine (center), and 3 minutes after Vaponefrin × 6 aerosol (right).

Subsequently 0.1 mg. Mecholyl i.v. was given, and a further reduction in T.V.C. and a rise in venous pressure were recorded. Twenty minutes later, the T.V.C. remained the same, the venous pressure had dropped, the air-flow rates decreased further and the intraesophageal pressure difference was nearly double the control recording. The patient was audibly wheezing. Finally Vaponefrin aerosols were given with marked improvement of all the values over the control state.

Computations of the mechanical resistance to inspiratory and expiratory

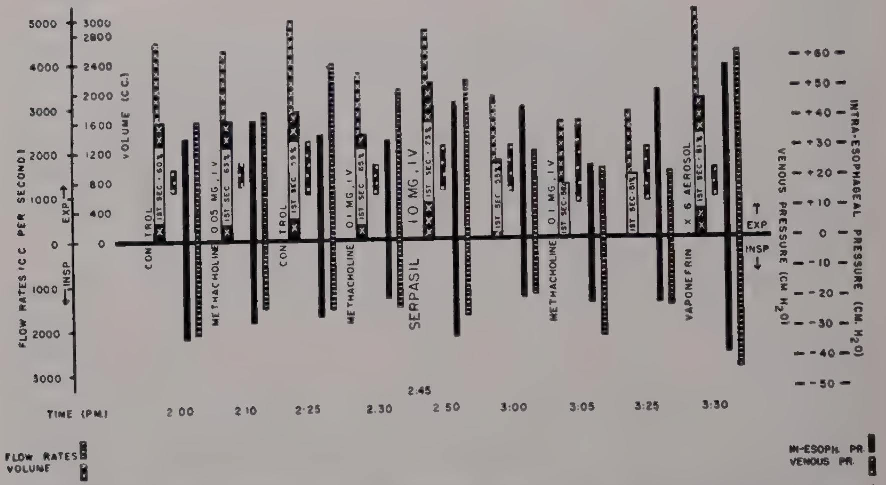

FIGURE 4. The effect of reserpine 1.0 mg. i.v. on induced bronchoconstriction. Simultaneous recordings of venous pressure, intraesophageal pressure, and pneumotachogram (air flow rates) during the timed vital capacity maneuver.

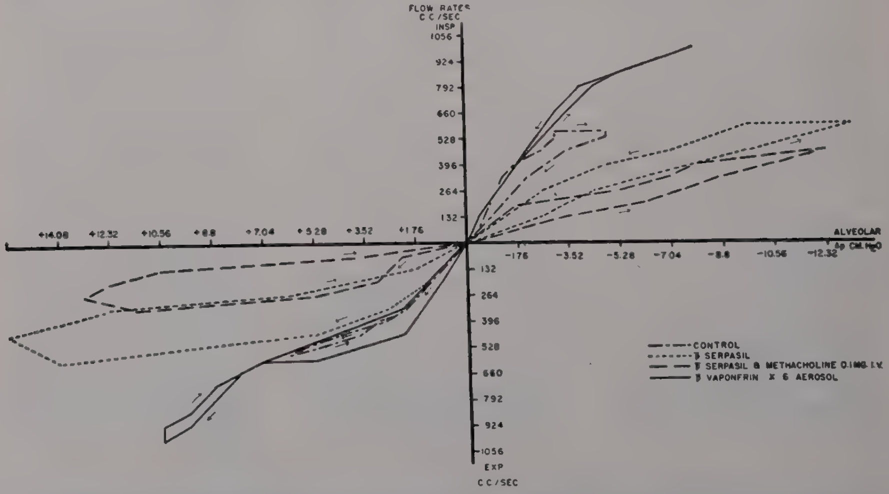

FIGURE 5. The effect of reserpine 1.0 mg. i.v. on the mechanical resistance of air flow in a patient with chronic bronchial asthma.

air-flow rates throughout the entire respiratory cycle were made from the data recorded in this patient, and appear in FIGURE 5. These data reveal a marked increase of mechanical resistance after reserpine, and a still further increase after the administration of Mecholyl. The mechanical resistance is actually restored to a somewhat better than control value after the administration of bronchodilator aerosols.

Conclusions

In this patient with chronic bronchial asthma, no adequate protection by i.v. reserpine against the bronchospastic effects of Mecholyl was noted. The effects were essentially additive to that of the Mecholyl. Considerably greater intrapulmonary pressure differences were required to move air in and out of

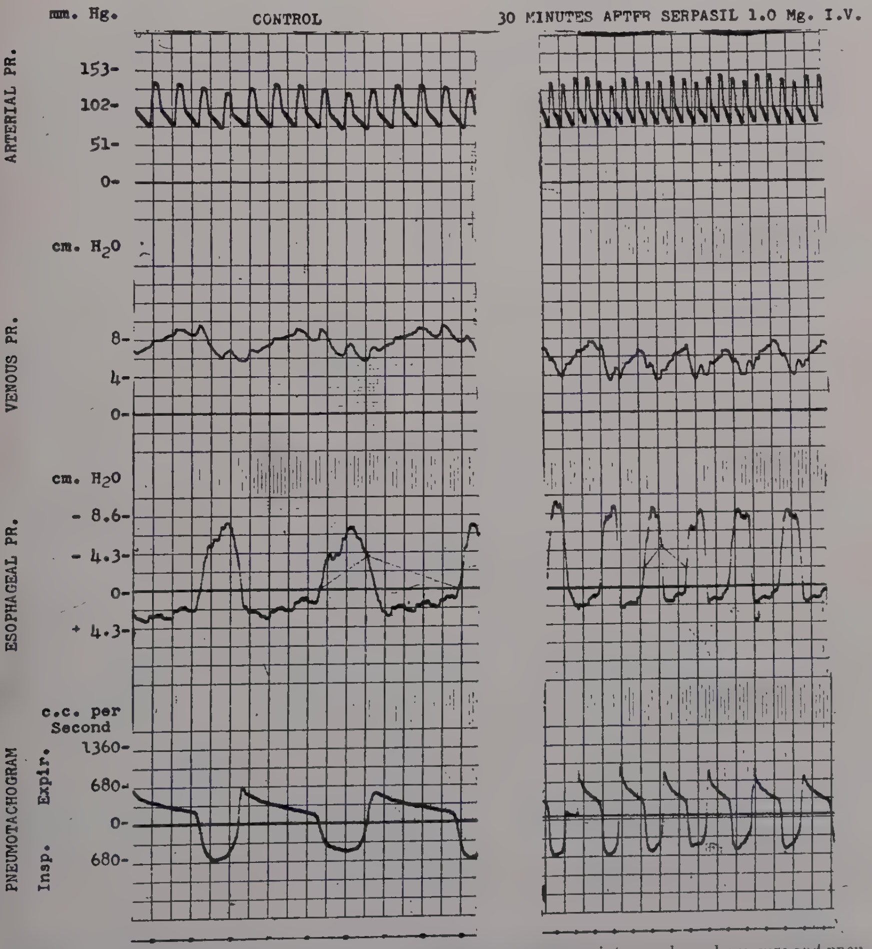

FIGURE 6. Simultaneous recordings of arterial pressure, venous pressure, intraesophageal pressure and pneumotachograph before (left) and 30 minutes after reserpine 1.0 mg. i.v. (right).

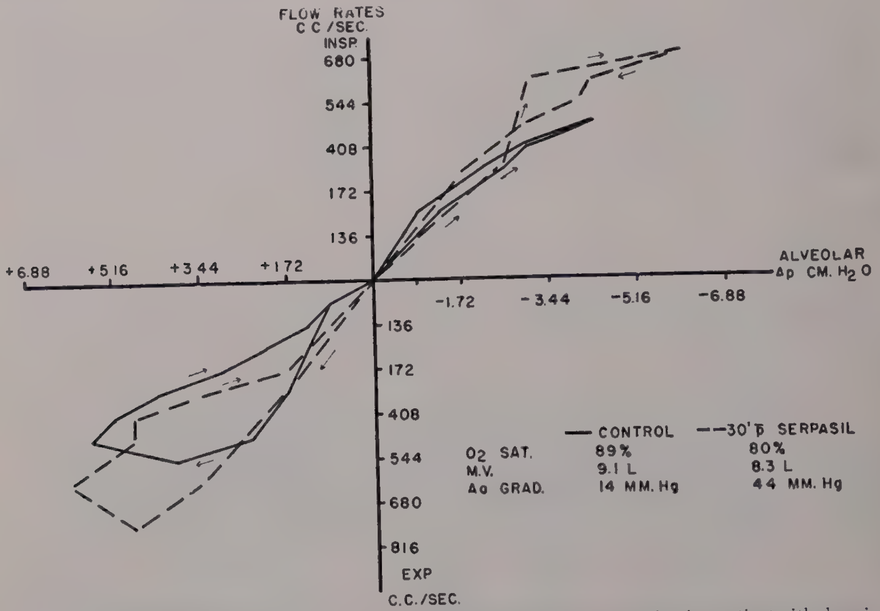

FIGURE 7. The effect of reserpine 1.0 mg. i.v. on the mechanical resistance of air flow in a patient with chronic pulmonary emphysema.

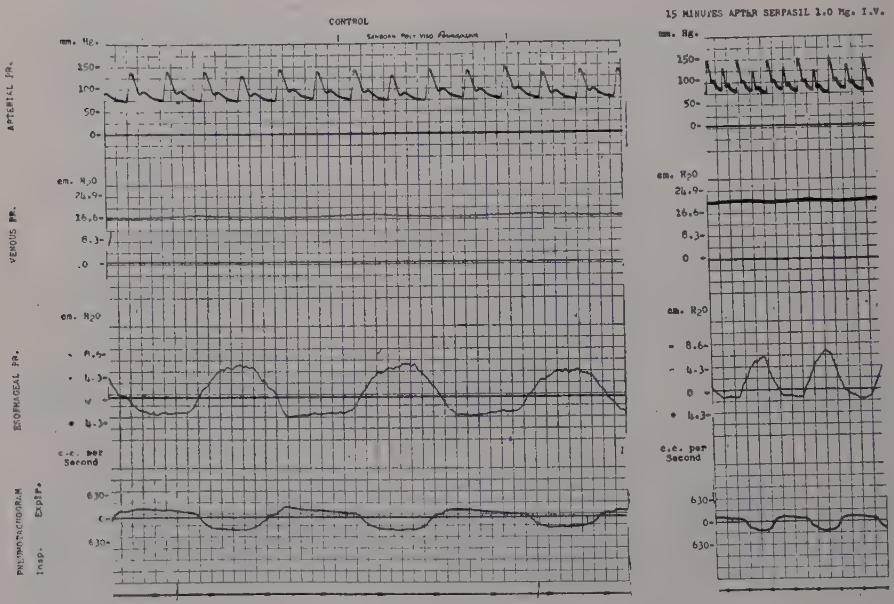

FIGURE 8. Simultaneous recordings of arterial pressure, venous pressure, intraesophageal pressure, and pneumotachograph before (left) and 15 minutes after reserpine 1.0 mg. i.v. (right). Note: Pulsus alternans more marked after reserpine. Rate of paper speed; control, 25 mm. per second; after reserpine, 10 mm. per second.

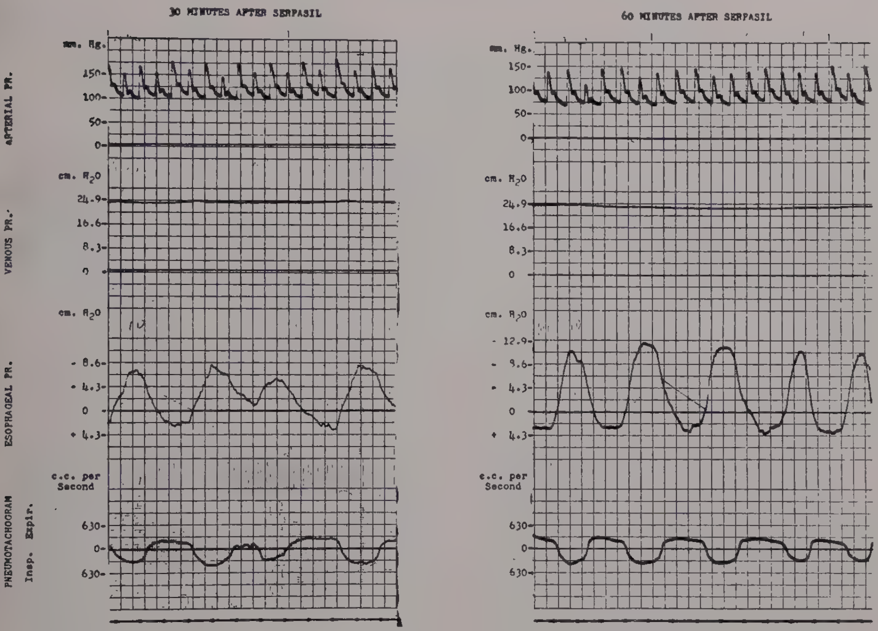

FIGURE 9. Simultaneous recordings of arterial pressure, venous pressure, intraesophageal pressure, and pneumotachograph 30 minutes (left) and 60 minutes (right) after reserpine 1.0 mg. i.v.

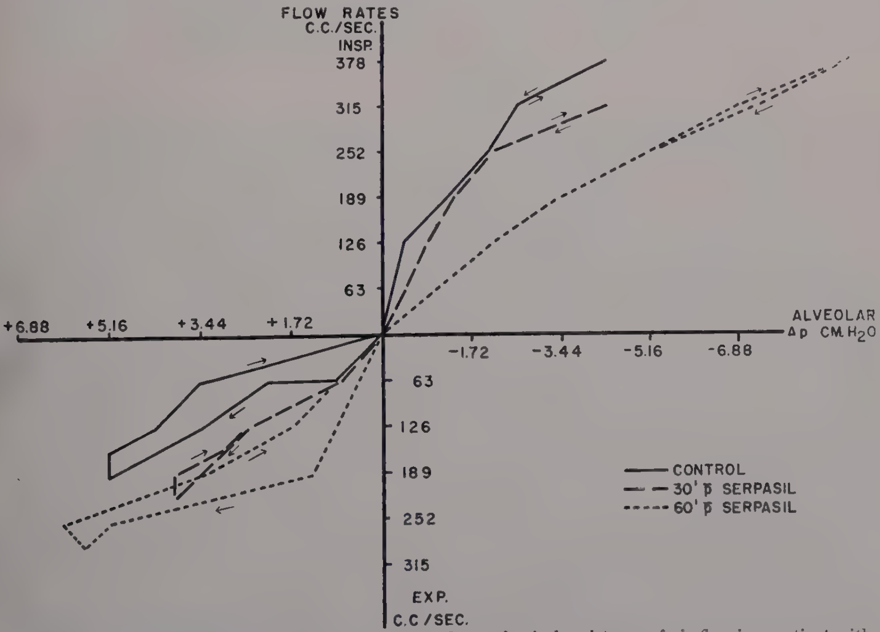

FIGURE 10. The effect of reserpine 1.0 mg. i.v. on the mechanical resistance of air flow in a patient with chronic pulmonary emphysema.

the lungs after reserpine. This indicates an increase of mechanical resistance to air flow and therefore an increase in the work of breathing.

Acute changes in the cardiopulmonary hemodynamics were studied in two patients with chronic pulmonary emphysema, not related to chronic bronchial asthma. *In one patient, M. F.*, a 59-year-old male with long-standing chronic pulmonary emphysema and recently developed cor pulmonale, the data are recorded in FIGURES 6 and 7. A study of the arterial blood gases in this patient before and after the administration of 1 mg. reserpine, i.v., revealed the following changes: a drop in arterial oxygen saturation from 88 volumes per cent to 80; an increase in the alveolar-arterial oxygen gradient from 14 mm. Hg to 44; and a drop in the minute volume from 9.1 liters to 8.3 liters. There were no significant changes in the arterial pCO_2 and pH.

Computation of the mechanical resistance (relation of alveolar pressure to air-flow rates) does not reveal any striking significant changes after reserpine, compared to the control state (FIGURES 6 and 7).

A second patient, D. M., a 55-year-old male with chronic pulmonary emphysema not related to chronic bronchial asthma, was studied in a similar manner (FIGURES 8, 9, and 10). After i.v. reserpine we noted a decrease to mechanical resistance in expiratory flow rates but an increase to the mechanical resistance in inspiratory flow rates. This indicates a more difficult inspiration but a more facile expiration.

An actual reduction in the work of breathing was calculated in both of these patients with chronic pulmonary emphysema. This reduction appears to have been achieved at a cost of an increase in alveolar-capillary insufficiency in the first patient, in view of the drop in arterial oxygen saturation, increase in alveolar-arterial oxygen gradient, and drop in minute ventilation.

Discussion

The *clinical data* with oral reserpine revealed that the drug appeared to be fairly well received and tolerated by the patients. Particular value was noted in the "alert state" and in patients with wide mood and personality swings. The annoying "stuffy nose" and "tight chest" were noted more commonly in patients with chronic bronchial asthma and less frequently in those with chronic pulmonary emphysema. Nasal vasoconstrictors and potassium iodide were helpful in relieving these side reactions.

The *physiologic studies* revealed the failure of i.v. reserpine to protect one patient with chronic bronchial asthma against the bronchospastic effects of Mecholyl. In fact, the effects of the latter were potentiated by the reserpine, as noted by the reduction in T.V.C. and the greater intrapulmonary pressure difference required to move air in and out of the lungs. In the two patients with chronic pulmonary emphysema, a reduction in the actual work of breathing was calculated. This was accomplished, however, at the high cost of an increase in alveolar-capillary insufficiency in the first patient.

The clinical side effects of stuffy nose and tight chest noted largely in the patients with chronic bronchial asthma and the failure of reserpine to protect against the experimentally induced bronchoconstriction with Mecholyl is probably due to cholinergic properties contained in the reserpine moiety. We have observed similar effects with cholinergic agents in our studies with experimentally induced bronchoconstriction in subjects with chronic bronchial asthma.[1] This may explain the somewhat better clinical and physiologic results noted in this study in the patients with chronic pulmonary emphysema.

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THE TREATMENT OF HEADACHE WITH RESERPINE

By Arnold P. Friedman

Headache Clinic of the Division of Neurology and Psychiatry, Montefiore Hospital; and the Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, N.Y.

The large number of therapeutic agents recommended for chronic headache, each year, indicate that the optimistic results reported from the primary investigator is not often substantiated on subsequent tests. In fact, prevention of chronic headache by use of drugs, with few exceptions, has been uniformly unsuccessful. Therefore, any new drug which may be of value in the prevention of chronic headache warrants investigation.

For many years, it was known in India that the plant *Rauwolfia serpentina* had a sedative and antihypertensive effect. Recently, it was demonstrated in the United States that reserpine, a chemically pure derivative of *Rauwolfia serpentina*, was the chief active alkaloid in the plant and one that can be used safely and effectively as a tranquilizer and antihypertensive agent.[1] Since this compound is said to exert its effect through action of the hypothalamus, which is associated so closely with the stress mechanism, it was thought advisable to study the action of this drug in patients suffering from migraine, tension, and hypertensive headaches. The purpose of this presentation is to report the results of such therapy on 150 patients during a one-year period.

Since the effectiveness of reserpine was said to vary in these specific groups of chronic headache, it is important to define clearly the diagnostic categories used. These are:

DIFFERENTIAL DIAGNOSIS

(1) *Migraine*

(a) *Clinical picture.* Migraine may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral, and throbbing. The headache occurs against a background of relative well-being, is often preceded by visual or psychological disturbances, and is usually associated with vomiting and irritability.

(b) *Physiological mechanisms.* The following physiological changes occur in an attack of migraine:[2] an initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other preheadache phenomena prior to the onset of the headache. This prodromal period is followed by dilatation and distention of cranial arteries, primarily in the distribution of the external carotid artery. Stimulation of pain-sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilatation results in a rigid, pipelike state of the vessels. The pain at this stage is a steady ache replacing the earlier throbbing, pulsation type. During or following this stage, there is contraction of the neck muscles, and "muscle-contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the headache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter, or "muscle pain," is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although, in migraine, the immediate cause of pain is associated with dilation of cranial arteries, it is evident that dilatation of blood vessels alone is not sufficient to produce headache. Other dynamic or chemical factors as yet not clearly delineated must contribute.

(2) *Tension Headache*

(a) *Clinical picture.* Tension headache occurs in relation to constant or periodic emotional conflict, of which the patients are usually partially aware. They have no prodromata, are usually bilateral, occipital, or frontal, and may be accompanied by a variety of associated signs including anxiety and nausea. Frequency and duration are variable.

(b) *Physiological mechanisms.* In tension headaches, muscular or vascular mechanism may act independently or concomitantly.[3] With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia, which could be a contributory or primary factor in the induction of pain. It has also been hypothecated that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory factor of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face. Under stress, a discharge may occur in the autonomic nervous system with resultant changes in the cranial blood vessels. The end organs for pain surrounding these blood vessels are stimulated and create nerve impulses which pass along the afferent pathways to the central nervous system.

(3) *Hypertensive Headache*

(a) *Clinical picture.* The headache of arterial hypertension is usually a dull, throbbing, deep ache. It is aggravated by strain, stooping, and emotional tension. This headache may be generalized or confined to the front or back of the head. Although usually bilateral, it may resemble migraine by periodicity and by being confined to one side of the head. It often appears upon the awakening of the patient and may improve as he moves about. Nausea and vomiting are infrequently noted. Another variety of headache occurring with hypertension is a suboccipital tightness and rigidity which may encircle the head.

(b) *Physiological mechanisms.* The pathogenesis of headache in essential hypertension is obscure. We do know that the degree of headache is not proportional to increased blood pressure. The headache may be present when the blood pressure is low as well as high. It is postulated that the variations in the contractile state of the cranial arteries is responsible for the headache, and that the elevated blood pressure is only an accessory factor. Experimental administration of ergotamine tartrate usually abolishes the headache, which would indicate that the mechanism of pain production may be similar to migraine. This headache is not due to increased intracranial pressure since this pressure is normal, nor will elevating it experimentally produce the head pain. There is no relationship to impairment of renal function in hypertensive headache. When the blood pressure is lowered by therapeutic measures such as sodium restriction or antipressor drugs, the headache disappears.

MATERIALS AND METHODS

The 150 patients in this group were selective in that they did not respond to their previous standard medical or psychiatric treatment. The symptoms were severe and tenacious. Diagnostically they were divided into the following groups:

(1) Migraine	37 cases
(2) Tension headache	80 cases
(3) Hypertensive headache	33 cases

The majority of the patients were females (94 females and 56 males). The age group ranged from 21 to 65 years of age, with the majority in the 4th decade. On the average, the symptoms were present for five years.

Since the action of reserpine taken orally is cumulative and slow, it was used as a preventive or prophylactic medication and not for symptomatic treatment. The average daily maintenance dose was 0.75 mg. orally. In many cases, however, patients were effectively stabilized at 0.5 mg. There seemed to be no appreciable difference in the end results, whether the patient was loaded in the beginning of therapy, or whether saturation was achieved slowly on a constant dose. Maximal effective action, in most cases, was obtained after 7 to 10 days on therapy. The drug was well tolerated, and only mild side effects were noted. Sleepiness and dryness of the nasal mucosa, nausea, and diarrhea were complained of in a small number of patients after maintenance was established. No evidence of addiction was noted.

Patients with hypertension showed a reduction mainly in the systolic blood pressure with a small reduction in the diastolic blood pressure, while the normotensive patients showed little or no blood pressure changes. The patients were observed for too short a time to evaluate the antihypertensive effect of reserpine. In general, the patients described themselves as being less tense and able to overlook many usually disturbing elements in their everyday activities. A few patients reported weight gain.

RESULTS

In evaluating a drug, we are aware that the efficiency of any drug does not depend upon its pharmacological action alone.[4] The importance of dosage, timing, mode of administration, and toleration by the patient can not be stressed sufficiently. Furthermore, such efficiency depends upon the patient-physician relationship, which includes, among other things, the length and frequency of interviews. Our experience indicates that a patient's reactions to drugs may depend not only upon the underlying disorder responsible for the headache, but also upon the degree of incapacity, constitutional make-up of

TABLE 1
TREATMENT OF HEADACHE WITH RESERPINE

Type of headache	No. patients treated	Patients' response					
		Good	%	Fair	%	Poor	%
Migraine	37	10	27	6	16	21	57
Tension*	80	22	27	28	35	30	38
Hypertensive	33	23	70	6	18	4	12

* Placebo level—55%.

the patient, duration of symptoms, age of individual and psychological status. The symbolic effect of taking a prescribed drug is also a contributory factor in treatment. All these factors must be given serious consideration in clinical usage of drugs in treatment of headache.

The results are summarized in TABLE 1. The patients were followed for a period ranging from two to eight months. In the 37 migraine patients, no effective results were achieved. Twenty-one received no relief, 6 reported reduced frequency of their attacks, and 10 received moderate relief. These poor results are due to the fact that, in migraine, sustained attitudes and emotional states provide the basis for the sequence of physiological changes which end in headache. Therefore, it is unlikely, in most cases, that reserpine, as now used, can produce the essential psychological changes needed in the patient to alter materially the course of their headaches.

In the 80 patients with tension headache, 22 showed considerable improvement in their headache status, 28 moderate improvement and, in 30 patients, no relief was obtained. These results must be considered in light of our previous favorable placebo response in 55 per cent of tension-headache patients.

In the 33 patients with hypertensive headaches, 23 showed marked reduction in the frequency of their headaches, 6 reported moderate improvement, and 4 showed no change in their headache status. In the four patients who obtained no relief, there was a reduction in the blood pressure similar to those who reported improvement.

These patients were all essential hypertensives. The average systolic pressure was about 180, and the diastolic about 100. The highest systolic pressure was 240, and the diastolic 150.

DISCUSSION

Past experience has indicated to us that most headaches result from an altered state of certain vascular and muscular tissues within and outside the cranium as part of the reaction of the individual to life's stresses. Chemical agents usually reduce or abolish the headache during the acute phase but rarely control the problem for a long period. The present report is entirely too short a survey in treatment time to evaluate final results.

SUMMARY

Reserpine was given orally to 150 patients with chronic headaches. Patients with hypertension showed considerable improvement; those with tension head-

ache, moderate improvement; and those with migraine, no definite relief. The present report is too short a survey in treatment time to draw final conclusions as to the effectiveness of reserpine in the treatment of chronic headache.

ACKNOWLEDGMENT

The author expresses his acknowledgment to Doctor Henry Doubilet for his suggestions.

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